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DIABETIC COMA

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The conquest of diabetic coma is in sight. During 1929 and 1930 in Stettin, Germany, with a population of 270,000, there was not a single death from diabetic coma.[1] Boston cannot make so good a showing, but the following letter from the health commissioner of the city speaks for itself:

March 31, 1936.

My dear Dr. Joslin:

I am happy to report to you that in the City of Boston during 1935 there was not a death from any cause whatsoever in a diabetic under nineteen years of age. During this twelve month period there were in all 288 deaths classified as diabetes and I understand including those with diabetes as a secondary cause 301 deaths.

Yours very truly,
(Signed) William B. Keeler, M.D.
Health Commissioner

In this twelfth paper on diabetic coma we shall (1) present 42 new cases, bringing to 318 the total number of patients treated since 1923; (2) discuss various considerations for the classification of cases of coma which will allow a better comparison of treatment by different methods; (3) describe in detail 3 fatal cases—in 1 the condition was mistaken for insulin shock and no insulin was given, death taking place three hours after the patient was admitted to the hospital, and in the other 2 death occurred from infections eight and twenty days, respectively, after recovery from the coma; (4) report on the respiratory metabolism in a case of diabetic coma, and, finally, (5) compare the results of our methods of treatment of diabetic coma in 54 children

From the George F. Baker Clinic, Elliott P. Joslin, M.D., medical director, at the New England Deaconess Hospital.

1. Gottschalk, A.: Das Stettiner System der Diabetikernachsorge, Klin. Wchnschr. **10**:704 (April 11) 1931.

entering the hospital with a carbon dioxide-combining power of the venous plasma of 15 volumes per cent or less, with 1 death (1.9 per cent mortality), with the results of treatment with methods recently proposed in this journal by Hartmann,[2] who reported on 27 patients with an initial plasma carbon dioxide content of 15 volumes per cent or less, with 5 deaths, or an 18.5 per cent mortality, and 15 patients (of the 27) treated with sodium lactate, with 2 deaths, or a 13.3 per cent mortality.

FORTY-TWO NEW CASES OF COMA

To the 276 cases of coma reported by us [3] between 1923 and October 1934 we now add 42 cases [4] in 41 patients treated in the fifteen months between Oct. 6, 1934, and Jan. 1, 1936. Six of the patients have been considered as "coma offenders" in our previously published series. In table 1 are recorded in detail the data regarding the 42 cases and in table 2 a summary of this and the preceding six series.

The average age in the present series was 28.2 years. The oldest patient was 66.5, and the youngest was 2.4 years of age. Twenty-seven of the patients were females and 15 males. The preponderance of coma in females has been consistent in each series. It has already been pointed out that this occurs in the ages in which the preponderance of cases of diabetes is in males. It is theoretically possible that hyperactivity of the pituitary gland during catamenia or during pregnancy may account for this. Thus, 6 women of our entire series of patients with coma, including 2 in the present group, had the attack during pregnancy.

The average duration of diabetes prior to the onset of coma was five and three-fifths years. The average sugar content of the blood when the patient was admitted to the hospital was 0.54 per cent, and this had fallen to 0.2 per cent on the second and to 0.19 per cent on the third day. In 3 of this series of 42 patients the initial sugar value was over 1,000 mg. per hundred cubic centimeters of blood. Two of the 3 patients (cases 13 and 38) recovered. The average carbon dioxide-combining power of the plasma was 11 volumes per cent. It rose to 30 volumes per cent on the second and 41 volumes per cent on the third day. In 11 patients the carbon dioxide-combining power of the plasma at the time of the patient's admission to the hospital was less than

2. Hartmann, A. F.: Treatment of Severe Diabetic Acidosis, Arch. Int. Med. **56**:413 (Sept.) 1935. See table 1 on page 415 for data for 12 patients with a plasma carbon dioxide content of 15 volumes per cent or less and for 3 others mentioned in footnote 1 *a*, page 414 (patients treated with sodium lactate).

3. Marble, A.; Root, H. F., and White, P.: Diabetic Coma, New England J. Med. **212**:288 (Feb. 14) 1935. See this article for earlier references.

4. One case was not included, although the carbon dioxide-combining power was 19 volumes per cent, because the urine was sugar-free, owing to treatment in another hospital before transfer to us.

TABLE 1.—*Data for Forty-Two Consecutive Cases of Diabetic Coma*

TABLE 1.—*Data for Forty-Two Consecutive Cases of Diabetic Coma*

Case No.	Age at Time of Coma, Years	Duration of Diabetes, Years	Date, 1934	Clinical Data: Kussmaul Respiration	Clinical Data: Mental Condition*	Blood: Sugar, % Day 1	Blood: Sugar, % Day 2	Blood: Sugar, % Day 3	Blood: Plasma CO_2-Combining Power, Vol. % Day 1	Blood: Plasma CO_2-Combining Power, Vol. % Day 2	Blood: Plasma CO_2-Combining Power, Vol. % Day 3	Blood: Nonprotein Nitrogen, Mg. per 100 Cc. Day 1	Blood: Nonprotein Nitrogen, Mg. per 100 Cc. Day 2	Blood: Nonprotein Nitrogen, Mg. per 100 Cc. Day 3	Urine: At Entrance: Diacetic Acid	Urine: At Entrance: Sugar, %	Urine: Sugar-Free After Entrance, Hours	Insulin Units Day 1	Insulin Units Day 2	Insulin Units Day 3	Comment and Result
1	35.2	9.2	Oct. 6	+	D	0.57	0.17	0.08	3	30	..	64	..	32	+	4.8	..	330	120	115	Thyroid storm
2	39.1	8.1	Oct. 15	+	D	0.82	0.08	0.24	2	33	..	75	36	..	+	2.8	14	410	60	64	
3	14.3	5.7	Oct. 16	+	D	0.65	0.21	....	8	35	..	54	..	..	++	5.4	9	185	50	67	
4	2.9	1.1	Oct. 25	+	D	0.40	0.32	....	2	..	..	..	..	..	+++	6.0	13	114	40	32	
5	27.5	1.8	Nov. 3	0	C	0.37	....	0.29	19	..	..	22	..	..	+++	4.0	..	65	54	64	
6	50.2	2.1	Nov. 8	+	C	0.38	0.09	....	11	42	..	40	..	..	+++	3.0	15	225	66	52	Pulmonary tuberculosis
7	15.0	2.7	Nov. 10	+	C	0.00	0.12	....	11	28	..	..	39	..	++	3.3	8	205	110	70	
8	49.4	9.5	Nov. 18	+	C	0.31	0.42	0.07	14	30	..	..	..	26	+++	3.8	5	110	68	75	
9	13.7	6.9	Dec. 2	+	C	0.11	0.23	0.16	20	17	..	..	32	..	++	2.5	13	145	70	76	
10	31.2	4.1	Dec. 11	+	C	0.54	0.29	....	6	30	..	..	33	..	+++	4.0	7½	120	75	60	
11	48.5	12.0	Dec. 24	+	D	0.54	0.32	0.26	4	37	59	..	38	29	++	3.3	12	345	60	64	
12	13.9	2.2	Dec. 30 1935	+	U	0.51	0.24	....	4	18	..	45	27	..	++++	3.4	4	190	85	70	
13	19.3	6.8	Jan. 7	+	U	1.58	0.06	....	<1	35	..	49	..	..	++++	6.0	11½	515	55	110	
14	16.2	4.6	Jan. 8	+	C	0.75	0.02	0.04	4	30	..	47	..	..	++	6.4	..	260	100	52	
15	33.7	4.6	Jan. 8	+	C	0.26	0.25	0.32	16	30	25	..	..	23	Trace	0.9	..	120	100	95	Labor and pneumonia
16	15.3	3.5	Jan. 9	+	C	0.29	0.19	....	8	29	..	34	27	..	+++	3.6	..	90	70	60	
17	66.5	2.7	Feb. 9	+	C	0.44	0.33	0.28	15	31	..	..	..	35	+	3.8	..	111	45	56	Fatal
18	39.8	11.7	March 3	+	D	0.51	0.16	0.23	14	29	..	..	34	..	++	5.4	20	285	75	70	
19	2.4	0.1	March 5	+	C	0.35	0.18	....	6	..	..	..	..	..	++	5.6	..	16	10	12	
20	32.7	5.0	March 13	+	C	0.53	0.07	0.32	17	39	..	36	21	..	++++	4.0	..	80	49	40	
21	6.6	0.1	April 5	+	C	0.44	....	....	9	..	..	..	..	..	+++	7.8	9	78	36	34	
22	34.8	12.8	April 19	+	C	0.58	0.09	....	10	..	..	..	..	..	+++	3.5	..	270	65	40	Pregnancy
23	14.1	7.5	April 29	0	C	0.22	0.38	0.23	18	..	..	40	..	..	+++	0.6	..	140	66	70	
24	65.6	4.1	July 8	+	U	0.59	0.26	0.08	7	24	21	..	63	46	0	2.0	32	480	40	30	
25	37.4	3.9	July 9	+	D	0.54	0.18	0.24	4	25	..	49	31	..	++	2.3	12½	276	54	46	
26	18.1	4.9	July 21	+	D	0.85	0.16	....	12	34	..	..	..	..	+	2.4	19	430	75	55	
27	15.2	1.8	July 22	+	C	0.32	0.17	0.07	15	..	..	30	..	..	++	2.4	6	120	70	62	
28	13.2	7.3	Aug. 3	+	D	0.30	0.13	0.23	17	20	..	..	33	..	+++	0.4	6	70	54	52	
29	10.7	4.5	Aug. 14	+	C	0.80	0.06	....	2	30	..	..	..	..	++	1.7	11	220	154	46	
30	8.7	0.7	Aug. 29	+	D	0.31	0.09	0.03	6	21	..	..	26	..	++	1.7	12	66	32	14	
31	12.4	0.3	Sept. 9	+	C	0.37	0.25	....	19	45	..	24	..	..	++	2.8	..	120	52	46	
32	42.3	13.3	Sept. 19	+	U	1.23	....	....	2	..	..	100	..	..	0	1.5	..	...	...	...	Fatal
33	20.0	7.6	Oct. 4	+	C	0.39	0.06	....	15	41	..	..	..	..	++++	8.0	..	130	60	60	
34	33.7	6.3	Oct. 10	+	S-C	0.61	0.40	0.11	15	28	..	44	41	..	+++	2.3	13½	200	35	55	
35	47.8	3.1	Oct. 12	+	D	0.37	0.17	0.02	18	27	..	..	..	..	++	2.8	10	138	52	84	
36	32.8	4.4	Nov. 3	+	S-C	0.60	0.05	....	12	20	..	..	..	..	+++	4.8	3	400	20	50	
37	24.3	10.3	Nov. 3	+	D	0.56	0.21	....	13	35	..	..	..	..	+++	4.2	7	265	30	60	
38	30.0	13.7	Nov. 8	+	S-C	1.07	0.11	0 05	4	19	58	70	..	..	0	3.9	14	510	105	80	Varicella
39	35.9	0.4	Nov. 25	+	C	0.33	0.24	0.26	18	38	..	50	36	..	++++	5.0	4	170	45	57	
40	43.0	5.9	Dec. 13	+	C	0.65	0.33	....	14	44	..	..	..	..	+++	6.0	8	210	36	64	
41	13.8	7.5	Des. 18	+	C	0.50	0.36	0.47	16	34	44	..	38	..	+++	4.8	8	155	70	72	
42	57.2	10.7	Dec. 20	+	..	0.42	0.27	....	17	23	..	..	34	..	+++	2.7	15	245	180	135	Fatal

* U indicates unconsciousness, with the patient unresponsive even to strong stimuli; S-C, stupor, with the patient responsive to strong stimuli; D, drowsiness and stupor; C, consciousness, with the patient in most instances, however, somewhat clouded mentally.

TABLE 2.—*Comparative Data, by Averages, for Seven Series of Cases of Diabetic Coma* *

Series	Number of Cases	Age at Time of Coma, Years	Duration of Diabetes Mellitus, Years	Date	Blood: Sugar, % Day 1	Blood: Sugar, % Day 2	Blood: Carbon Dioxide-Combining Power of Plasma, Vol. % Day 1	Blood: Carbon Dioxide-Combining Power of Plasma, Vol. % Day 2	Blood: Carbon Dioxide-Combining Power of Plasma, Vol. % Day 3	Blood: Non-protein Nitrogen, Mg. per 100 Cc. Day 1	Urine at Entrance: Diacetic Acid	Urine at Entrance: Sugar, %	Insulin, Units Day 1	Insulin, Units Day 2	Insulin, Units Day 3	Fatal Cases: Number	Fatal Cases: Percentage
1	24	31.5 (24)	2.4 (24)	May 1923 to March 1925	0.47 (23)	0.20 (20)	15 (24)	33 (20)	31 (10)	47 (16)	++++ (24)	3.3 (24)	154 (24)	63 (22)	58 (21)	5	21
2	28	31.6 (28)	2.8 (28)	April 1925 to Feb. 1927	0.49 (28)	0.20 (20)	14 (28)	29 (20)	30 (10)	46 (21)	+++ (28)	3.4 (28)	166 (28)	59 (26)	49 (26)	4	14
3	53	29.1 (53)	4.0 (53)	March 1927 to Feb. 1929	0.53 (52)	0.21 (46)	13 (53)	28 (37)	38 (12)	60 (33)	+++ (53)	3.1 (53)	183 (53)	40 (50)	39 (50)	5	9
4	74	31.3 (74)	3.5 (74)	Feb. 1929 to Aug. 1931	0.49 (74)	0.20 (51)	11 (73)	29 (42)	35 (13)	48 (52)	++ (74)	3.7 (74)	252 (74)	49 (65)	41 (62)	13	18
5	42	26.1 (42)	3.5 (42)	Aug. 1931 to Oct. 1932	0.47 (42)	0.15 (37)	12 (20)	28 (28)	33 (5)	37 (17)	++ (42)	3.9 (40)	201 (42)	51 (41)	45 (39)	2	5
6	55	28.5 (55)	4.3 (55)	Oct. 1932 to Oct. 1934	0.51 (55)	0.17 (46)	12 (55)	29 (31)	34 (9)	49 (28)	++ (54)	3.6 (54)	196 (55)	52 (51)	44 (50)	6	11
7	42	28.2 (42)	5.6 (42)	Oct. 1934 to Jan. 1936	0.54 (42)	0.20 (39)	11 (42)	30 (34)	41 (5)	49 (18)	++ (42)	3.7 (42)	210 (41)	66 (41)	61 (41)	3	7

* The figures in parentheses indicate the number of determinations on which the average was computed for each series.

5 volumes per cent. Ten of the 11 recovered. It should be noted that the chemical values on the second and third days are for only a partial number of the entire series; often these values are not determined, since many patients recover so rapidly that later determinations seem needless. Possibly this fact was overlooked by Hartmann, who, on page 429 of his paper, stated that "a number of his [Joslin's] patients . . . still had marked acidosis on the second and third days of treatment."

The nonprotein nitrogen content of the blood when the patient was admitted to the hospital was more than 40 mg. per hundred cubic centimeters of blood for 12 of the 18 patients for whom the test was performed and 70 mg. per hundred cubic centimeters or more for 3.

The average of insulin prescribed in the first twenty-four hours of treatment was 210 units.

Dietary indiscretion was the most common etiologic factor, occurring in 12 cases. Five patients had omitted taking insulin. Four had not kept to their diet and had omitted insulin. In 7 cases infection was the inducing factor. Eight patients had unrecognized or inadequately treated diabetes, and in 2 the cause of coma was unexplained. In 4 cases the condition appeared to have been precipitated by endocrine complications. Thus, 1 patient (case 1) had combined "thyroid storm" and diabetic coma. She entered a surgical service of the hospital. The sugar content of the blood was 0.12 per cent, and the urine contained 2 per cent sugar at 7 p. m. At 7 the next morning the sugar content of the blood was 0.57 per cent, and the carbon dioxide-combining power was 3 volumes per cent. Two patients were pregnant, and the pregnancy in 1 was complicated by lobar pneumonia. She was delivered normally of a nonviable infant. The other (case 22) had early toxemia of pregnancy, and the uterus was emptied at the ninth week. One child (case 23) entered in coma with the onset of her first catamenial period.

Eighteen of the patients belonged to our juvenile series (*onset of diabetes at 15 years of age and under*). This increases the number of patients in coma in the juvenile series to 134 treated since 1923; of these, 133 recovered. Among 1,000 patients in whom the onset of diabetes was at the age of 15 years or earlier, a recent tabulation [5] showed that 300 had coma at some time in the course. This series included cases in which the disease developed in the preinsulin era, however, and of the last 400 patients seen, only 46 had had coma at some time in their diabetic life.

Clinical Considerations.—Only 4 of the 42 patients were totally unconscious. Kussmaul breathing was present in all but 2 patients.

5. White, P., in Joslin, Elliott P.: The Treatment of Diabetes Mellitus, ed. 5, Philadelphia, Lea & Febiger, 1935, p. 509.

Diacetic acid was not present in the urine of 3 patients who had advanced acidosis and signs of renal block.

Complications.—In 10 patients complications included "thyroid storm," pregnancy and pneumonia, toxemia of pregnancy, pulmonary tuberculosis, otitis media, prostatic abscess, acute tonsillitis, severe varicella and acute infection of the upper respiratory tract.

Mortality.—The mortality rate in the present series was 7.1 per cent. The mortality rate for our 318 cases was 11.9 per cent (38 deaths). The age of the patient has a direct influence on mortality, as will be discussed later.

CLASSIFICATION OF CASES OF DIABETIC COMA

No one would think of comparing the results of treatment for pneumonia in patients above 60 years of age in one city with those in patients

TABLE 3.—*Data on the Rise in Mortality with the Advance in Ages of Patients in Diabetic Coma*

Age at Coma, by Decades	Total Number of Cases	Fatal Cases	
		Number	Percentage
First	23	0	0.0
Second	123	3	2.4
Third	38	3	8.0
Fourth	43	5	11.6
Fifth	38	7	18.4
Sixth	33	14	42.4
Seventh	16	5	31.3
Eighth	4	1	25.0
Total	318	38	11.9

less than 15 years of age in another city. The same applies to diabetic coma. The mortality among old persons with diabetic coma is high, but among 54 children (15 years of age or less at the time of coma) there has been but 1 death. Consequently, in any report on diabetic coma the treatment should be compared on the basis of age, and advice with regard to treatment should be based on experience with patients of different ages. Table 3 illustrates the general rise in mortality for coma from 0 in the first decade and 2.4 per cent in the second to 42.4 per cent in the sixth. Old age by no means invariably implies a fatal outcome, however. On Jan. 29, 1936, a woman, not included in this series, recovered from coma at 75 years of age, being two years older than our oldest patient previously recorded. The blood sugar value at the time of her admission to the hospital was 0.66 per cent, and the carbon dioxide-combining power of the plasma was 12 volumes per cent.

Without some criterion as to the extent of the acidosis it is impossible to compare different methods of treatment. In 1917, five years

before the introduction of insulin, one of us [6] reported on 15 patients in diabetic coma who recovered after showing a carbon dioxide tension of the alveolar air of 20 mm. of mercury or less. The carbon dioxide-combining power of the plasma of these patients ranged between 14 and 28 volumes per cent. These facts led to the use of a tension of the carbon dioxide of the alveolar air of 20 mm. of mercury and later a carbon dioxide-combining power of the plasma of 20 volumes per cent as an arbitrary dividing line between cases of precoma and cases of coma. The latter figure still remains a good point of division. In 9 of 91 patients in coma in our series with a carbon dioxide-combining power of the plasma between 16 and 20 volumes per cent, inclusive, death occurred. The mortality, 10 per cent, was about the same as for the entire series, and to exclude these 91 cases would result in the omission of some patients who were in serious acidosis. One might decide to omit cases in which there was a carbon dioxide-combining power of over 15 volumes per cent in order to stiffen the requirements. However, a carbon dioxide-combining power of 18 or 20 volumes per cent and a carbon dioxide content of 15 volumes per cent are nearly comparable values. Certainly the exclusion of cases in which the carbon dioxide-combining power was between 16 and 20 volumes per cent would exclude many fatalities; therefore, we hold to our present standard.

If there is any more accurate or better method of determining the depth of coma than the determination of the carbon dioxide-combining power or content of the blood plasma, certainly all should adopt it. We cannot accept the blood sugar or the nonprotein nitrogen content or the degree of glycosuria as an index, and the blood pressure is not distinctive enough. Unconsciousness is difficult to measure, depending as it does a good deal on the effort taken to arouse the patient. Therefore, it cannot be used as a set standard, although a record of the degree of unconsciousness should be made. So, too, the Kussmaul respiration varies in different stages. The longer the diabetic coma lasts, the less distinctive becomes the Kussmaul respiration, and during the last few hours before death it usually disappears.

THREE DEATHS IN COMA

1. *Diabetic Coma Mistaken for Hypoglycemia.*—A man (case 32) who was almost 29, a tea taster, learned that he had diabetes and began treatment on May 25, 1922. Fortunately for him he had married a nurse the preceding year. When he first consulted one of us (Dr. E. P. Joslin) seven months later, in January 1923, his weight when dressed was 111 pounds (50.5 Kg.), or about 42 pounds (19.1 Kg.) below the standard weight for his age and height. After his marriage his weight had risen to its maximum of 135 pounds (61.4 Kg.) at the onset of diabetes. At

6. Joslin, E. P.: Diabetes: The Results of Past Treatment and Future Problems, Bull. Johns Hopkins Hosp. **29**:82 (April) 1918.

first no history of diabetes was obtained, but later in an uncle and a cousin the disease developed. In January 1923 except for emaciation the physical examination revealed no abnormality. The Wassermann reaction was negative. The sugar content of the blood was 0.25 per cent (250 mg.), and the urine contained 2 per cent sugar. The urine became sugar-free with a low diet, and insulin treatment was begun within a few months. In 1924 the patient's weight had risen to 122 pounds (55.5 Kg.). He reported infrequently, and although he worked steadily and his weight rose to 127 pounds (57.7 Kg.) on Jan. 7, 1929, on a diet of 46 Gm. of carbohydrate, 74 Gm. of protein and 167 Gm. of fat, it was only with considerable insistence on our part that the carbohydrate of his diet was increased to 76 Gm. The dosage of insulin was 12, 0 and 12 units. The blood pressure was 96 systolic and 70 diastolic. On Jan. 17, 1933, his weight (dressed) was 131 pounds (59.5 Kg.). The urine showed diacetic acid; one specimen contained 2.7 and another 0.6 per cent of sugar. The blood sugar content was 0.24 per cent (240 mg.), the nonprotein nitrogen content 33 mg. and the cholesterol content 234 mg. per hundred cubic centimeters. The diet which he had been following contained 102 Gm. of carbohydrate, 77 Gm. of protein and 155 Gm. of fat. The dosage of insulin was 32 units a day. The blood pressure was 90 systolic and 60 diastolic. Two years intervened until his next visit on Jan. 15, 1934, his last before he entered the hospital eight months later. His weight (dressed) was 136 pounds (61.8 Kg.). The urine contained 2.3 per cent of sugar. The blood sugar content was 0.22 per cent (220 mg.) four hours after lunch, and the cholesterol value was 238 mg. per hundred cubic centimeters. The blood pressure was 112 systolic and 70 diastolic. The heart was normal except for a soft systolic murmur. Slight radial sclerosis was noted.

On Sept. 19, 1935, at 10: 50 p. m., the patient, a methodical, upright man, who was punctilious about his diet and insulin treatment, was admitted to the New England Deaconess Hospital unconscious and pulseless. Two days before he had gone on a business trip to New York, the first without his wife in the thirteen years he had had diabetes. After completing his business he took the afternoon train for Boston, and just before the train reached that city he became unconscious. From the train he was taken in an ambulance first to a suburban police station, 8 miles distant, and from there to his home, and then was brought to the hospital.

Although when the patient was admitted to the hospital the radial pulse could not be felt, a possible systolic blood pressure of 70 mm. was obtained. The heart rate was slow and regular, and the sounds were distant and of poor quality. The skin was cold, and the rectal temperature was 97 F. (36.1 C.). The respiration was regular, slow and labored. Nine grams of dextrose was given intravenously in 50 per cent solution at 11: 05 and again at 11: 20 p. m. His color improved, but the respiratory and pulse rates did not. At 11: 30 and again at 11: 40 p. m., 1 cc. of epinephrine hydrochloride, 1: 1,000, was given subcutaneously, with some elevation of the pulse rate. The patient moved a little. Nine grams more of dextrose was given intravenously at 11: 55 p. m. The respiration then became more rapid and less labored. At 12: 20 a. m. he apparently recognized his wife. At 12: 30 he was taking water from a spoon, and between 12: 30 and 12: 45 he swallowed 100 cc. of orange juice. His color was improving, but he continued groaning. At 1 a. m., though pulseless, he responded to 0.23 Gm. of caffeine with sodium benzoate. At 2 a. m. he died.

The gross observations at autopsy were acute dilatation and marked congestion of the stomach, and congestion of the lungs, with slight edema and fatty infiltration of the liver. Microscopic study confirmed the previous diagnosis, with the addition of subacute pancreatitis, deposition of glycogen in the nuclei of the hepatic

cells and in the renal tubules, fatty degeneration of the kidneys and hemorrhagic necrosis of the gastric mucosa. It is notable that the vessels of the heart were smooth and elastic; there were no emboli or thrombi. The aorta was normal, except for a slight degree of atheromatous degeneration in the abdominal portion. Yet this man had lived for thirteen years on a diet comparatively low in carbohydrate.

At the time of the patient's entrance to the hospital the blood sugar content was 1.23 per cent (1,230 mg.), the nonprotein nitrogen content was 100 mg. per hundred cubic centimeters and the two samples of blood plasma, pooled, showed a carbon dioxide-combining power of 2 volumes per cent. The fact that these extreme values were not known until after death occurred does not ease one's conscience that the patient died while being treated for hypoglycemia instead of diabetic coma. The blood sugar value of 1,230 mg. did not necessarily imply a poor prognosis, because we have noted 13 cases with 8 recoveries in which the blood sugar values were 1,000 mg. per hundred cubic centimeters or above when the patient was admitted. Dillon and Dyer [7] have recently reported 16 cases of diabetic coma in which the blood sugar content was 1,000 mg. or more when the patient was admitted to a ward of the metabolic department of the Philadelphia General Hospital. Five of the patients recovered, and 11 died. In Hartmann's [8] recent series of 91 (86 and 5) cases in children no case was mentioned in which the blood sugar value was over 922 mg. Only 27 had values for the carbon dioxide-combining power of 15 volumes per cent or less, yet 5 died. The nonprotein nitrogen content was 100 mg. per hundred cubic centimeters, but we have seen recovery in 3 of 7 cases in which the value was equal to or higher than that. It is true that the carbon dioxide-combining power was only 2 volumes per cent, yet in 9 cases in which there was such a value we have had 7 recoveries. The low blood pressure did not justify death. Consequently, in this case the condition was not clinically or chemically hopeless.

Urine was not obtained until at autopsy. It contained 1.5 per cent sugar and acetone but no aceto-acetic acid. Even if urine had been obtained when the patient was admitted to the hospital it would not have solved the differential diagnosis between coma and hypoglycemia, because often the first specimen of urine voided by the hypoglycemic patient contains sugar, having been secreted perhaps hours earlier by the kidneys.

Reasons for the Wrong Diagnosis: This patient was admitted to a floor of a hospital where at least 200 patients in diabetic coma have been treated in ten years. He was accompanied by his wife, a nurse.

7. Dillon, E. S., and Dyer, W. W.: Diabetic Coma with Extreme Hyperglycemia, Am. J. M. Sc. **190**:683 (Nov.) 1935.

8. Hartmann,[2] p. 418, table 3; p. 414, footnote.

He was promptly seen by a doctor, house officers and a night supervisor, who together must have observed at least 50 and probably 100 patients in coma, but all were so positive that this patient had hypoglycemia that they broke every rule and did not secure instant chemical verification of the diagnosis. Although a specimen of blood was taken at once and again one and one-half hours later, the report was delayed, in spite of the fact that we have arrangements by which examinations of blood can be made any time in the twenty-four hours. No urine was obtained, partly because the patient could not void and partly because of hesitancy in cases of coma in catheterizing a patient, due to the fact that infection of the genito-urinary tract is so common among diabetic patients.

If in a hospital to which more than 1,200 diabetic patients are admitted a year and which prides itself on its treatment of coma, such an error can occur, it is reasonable to infer that it may occur in other hospitals. An unconscious diabetic patient in any hospital must be surrounded with facilities, including personnel and methods, which will insure prompt chemical aids to diagnosis day or night. There must be a "coma-drill," just as much as a fire-drill. Substitute house officers must be examined for their ability to perform laboratory analyses in an emergency at night, and no matter how clearly correct the diagnosis and treatment may seem to younger doctors or house officers, their superiors must be informed and full responsibility assumed by them.

The fact that this patient had not been seen for eight months likewise should not be overlooked. A diabetic patient if he wishes to live should keep in touch with his physician. It is true that in 12.5 per cent of our last 981 fatal cases (up to March 13, 1935) the patient had lived for twenty years after the onset of diabetes. But this shows how careful one must be to follow up cases if one wishes to improve the percentage of survivals. This patient had had diabetes for thirteen years. He had at least moderately severe involvement. In the course of five years he had reported to us for examination only three times. A diabetic patient should report to his doctor at least every three months. This man had had reactions, and on his trip to New York he may have reduced the dosage of insulin to avoid them. However, if he had been more conversant with present methods of diet and treatment, he possibly would have averted an attack of coma. The diabetic patient must keep in touch with his physician. Physicians should not hesitate to follow up their patients who have had diabetes for a long time, even though sometimes it exposes them to criticism.

2. *Fatal Coma Precipitated by Infection in the Genito-Urinary Tract.*—A man (case 17) who was 63 at the onset of diabetes in June 1932, entered the New England Deaconess Hospital on Feb. 9, 1935. For three days he had complained of constipation, increasing weakness and deep breathing. At the time of the

patient's admission to the hospital respiration of the Kussmaul type was present, and his breath had an acetone odor. The blood pressure was 140 systolic and 68 diastolic. The blood sugar content was 0.44 per cent, and the carbon dioxide-combining power of the venous plasma was 15 volumes per cent. The urine contained 3.8 per cent sugar, 2 plus diacetic acid and a slight trace of albumin. The sediment was filled with white blood corpuscles. The prostate gland was enlarged and boggy. A partial intestinal obstruction developed, and a mass could be felt low down in the abdomen. He was relieved of diabetic acidosis easily with 52 units of insulin. However, the evidences of pelvic and renal infection with metastatic infection in the lungs precluded any surgical treatment. The nonprotein nitrogen content of the blood steadily rose and finally reached 105 mg. per hundred cubic centimeters, and the patient died eight days after entrance to the hospital. At autopsy large prostatic and periprostatic abscesses, with induration and inflammation of the tissue about the bladder, were present. Bilateral pyelonephritis with abscess formation and one perinephric abscess as well as nephrolithiasis and acute hemorrhagic and suppurative cystitis completed the involvement of the genito-urinary tract. The pancreas weighed 80 Gm.; many islands were partially hyalinized. Incidental observations included pulmonary abscesses, bronchopneumonia and a diverticulum of the duodenum. (Since the first report of 2 cases of duodenal diverticulum in diabetic patients by Thorning and Root,[9] 10 other cases have been discovered.)

The frequency and severity of genito-urinary infections in diabetic patients have not been appreciated generally. In 35 of 196 (18 per cent) autopsies at the New England Deaconess Hospital infection of the urinary tract of a serious nature was present.[10] Hematogenous infection, usually due to a streptococcus or a staphylococcus, was present in 25 cases. Ascending infection, usually associated with some type of obstruction, such as calculi or prostatic hypertrophy, was present in 5 cases, and in the remaining 5, including cases of pyelonephritis and renal abscesses, the origin could not be determined.

Three of these 35 patients had diabetic coma with a reduction in the carbon dioxide-combining power of the plasma to below 20 volumes per cent, and 4 had severe acidosis. The presence of ketone bodies in large amount had not seemed to exert any favorable influence in retarding the bacterial growth. Indeed, it is generally true that ketosis in a diabetic patient is associated with lowering of the resistance to infection. In these cases it appeared that genito-urinary infection had been present before the acidosis was recognized and that if it exerted any influence, it was in the direction of diminishing the resistance to the infection.

In diabetic patients infection with Bacillus coli is a serious menace, especially in older patients confined to bed by reason of a surgical operation. Paralysis of the bladder leads to back pressure and ascending infection. B. coli thrives at a p_H of from 6 to 7, according to Schohl

9. Thorning, W. B., Jr., and Root, H. F.: Diverticula of the Duodenum and Diabetes, Am. J. Digest. Dis. & Nutrition **2**:17 (March) 1935.

10. Sharkey, T. P., and Root, H. F.: Infection of the Urinary Tract in Diabetes, J. A. M. A. **104**:2231 (June 22) 1935.

and Janney,[11] but is inhibited at a p_H of from 4.6 to 5 and from 9.2 to 9.6. Possibly other factors are of greater importance when the diabetes is not under good control. Richardson [12] found that, regardless of the level of the blood sugar, the bactericidal property of the whole blood of diabetic patients was weaker than that of nondiabetic patients. Furthermore, after inoculation with typhoid vaccine a diabetic patient is less able to form agglutinins. Richardson suggested that this lowered resistance was due chiefly to a disordered state of cellular nutrition related to the diminished glycogen reserves. A lowered opsonin-producing power of diabetic blood has been reported by Horster [13] in depancreatized animals. Certainly the frequency and the insidious, often "silent" character of such infections in diabetic patients, especially in those with acidosis, is to be borne in mind constantly.

3. The Third Fatal Case in the Present Series and the Relation of the Condition to Trauma.—An American housewife (case 42) aged 58 entered the Deaconess Hospital on Dec. 20, 1935, in diabetic coma. The onset of diabetes was in May 1925. Diabetic coma in 1930 and a subsequent carbuncle had been treated successfully. In July 1935 a blister appeared on the end of the third right toe, and drainage from this area continued for several weeks, while the patient was not under our care.

The present illness began with a fall down four stairs on Dec. 16, 1935, when the patient twisted her right knee. The injury seemed at the time to be slight. She got up and did her usual work for that entire day. Alternate hot and cold applications were employed, not because of pain but to "prevent trouble." On the next day, however, the patient suddenly felt such severe pain in the knee that a physician who was called in gave morphine. A day later swelling of the leg and pain came on which prevented movement, and the patient was put to bed with the leg in an open cast.

Difficult breathing developed on about December 19, and on December 20 the patient entered the hospital in diabetic coma, with a carbon dioxide-combining power of the plasma of 17 volumes per cent and a blood sugar content of 0.42 per cent. The eyeballs were soft. The patient was not entirely unresponsive but was delirious and uncooperative. With 225 units of insulin and the usual treatment with gastric lavage and liquids, given both subcutaneously and intravenously, she made a good recovery.

On December 22 the third right toe was found to have become infected about and under a callus. The right knee was much swollen, as if fluid were present, and the presence of fluid was confirmed by roentgen examination. There was

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11. Schohl and Janney, quoted by Clark, A.: Escherichia Coli Bacilluria Under Ketogenic Treatment, Proc. Staff Meet., Mayo Clin. **6**:605 (Oct. 14) 1931.

12. Richardson, R.: Immunity in Diabetes: I. Influence of Diabetes on Development of Antibacterial Properties in Blood, J. Clin. Investigation **12**:1143 (Nov.) 1933; II. Relative Importance of Nutritional State and of Blood Sugar Level in Influencing Development of the Agglutinin After Typhoid Vaccine, ibid. **14**:389 (July) 1935.

13. Horster, H.: Beitrag zur Klärung der Ursache der verminderten Widerstandsfähigkeit des zuckerkranken Organismus gegen Infektion, Deutsches Arch. f. klin. Med. **176**:502 (July 9) 1934.

edema of the lower part of the leg but no evidence of lymphangitis. A blood culture was taken because of an afternoon fever, but no growth was obtained. Daily examinations of the patient were made in the search for a cause for the persistent afternoon rise in temperature, ranging to 100 or 101 F., and a leukocyte count of 19,000. On December 29 the entire right leg was swollen, and the right thigh was definitely larger than the left. At this time it did not seem that the infectious process in the knee accounted for the fever. There had been no break in the skin at the knee joint. The condition was thought to be due to phlebitis. A localized area of tenderness developed on the anterior aspect of the lower third of the thigh. On January 5 crepitus was felt in the knee joint, suggesting the presence of gas due to infection.

On January 7 purulent fluid was aspirated both from the knee joint and from the thigh. Streptococcus haemolyticus was grown from the fluid from both areas. About 6:15 that same evening the patient became faint, and her appearance was anxious. A black stool was passed the next day, but this was discounted as she had been receiving iron by mouth.

A blood transfusion of 750 cc. was given on January 8. On January 9 incision and drainage of the right thigh and knee joint were made so that the entire thigh was laid open. The joint capsule was observed to be destroyed by direct extension of infection from the knee joint into the thigh. The patient died at 8 o'clock in the evening, twenty days after recovery from diabetic coma.

The postmortem anatomic diagnosis was as follows: duodenal ulcer of large size in the first portion of the duodenum, with an artery projecting directly into the ulcer; much changed blood in the intestine, indicating a recent hemorrhage; many diverticula of the jejunum; healed appendicitis; fibrous adhesions of the cecum, and septic infection of the right knee and thigh. The pancreas weighed 60 Gm. and showed diffuse fibrosis and hyalinization of the islands of Langerhans. Fatty infiltration was abundant, and some lymphocytic infiltration was present.

THE RESPIRATORY METABOLISM IN DIABETIC COMA AND THE CARBON DIOXIDE CONTENT OF THE BLOOD

Among the many metabolic changes occurring in the patient suffering from advanced diabetic coma, certain features stand out with special prominence. One may here include the total energy exchange, changes in the body temperature with their effect on energy exchange, dehydration, changes in the base concentration of the blood and tissues consequent to vomiting and polyuria, changes in the chemical components of the blood and urine, the production of ketone bodies and their excretion through the lung and kidneys and changes in the function of the kidney. In the following case report data bearing on certain of these points will be presented.

A boy (case 38), aged 17 years, was found on Feb. 23, 1923, to have diabetes. He was first seen by us on March 8, at which time the urine contained 0.1 per cent sugar. He left the hospital in two weeks, taking 5 units of insulin three times a day, with a diet which included 158 Gm. of carbohydrate, 75 Gm. of protein and 120 Gm. of fat. At this time his net weight was 147 pounds (66.8 Kg.). On Oct. 4, 1927, the urine contained 0.3 per cent sugar. The patient was taking a diet of 91 Gm. of carbohydrate, 78 Gm. of protein and 138 Gm. of fat. The blood sugar value was 0.26 per cent. The dose of insulin was 20 units in the morning and 20

units before supper. In April 1929 a roentgenogram of the lungs showed a suspicious increase in the markings, but no definite diagnosis of tuberculosis was possible.

About Nov. 1, 1935, a rash broke out rather suddenly over the patient's face, scalp, trunk and extremities. He had had some acne previously. During the next week he felt rather weak and could not work; he remained at home. On November 7 difficulty in breathing and vomiting developed. The patient entered the Deaconess Hospital on November 8, at about 3:30 p. m., in profound diabetic coma, although he was not entirely unresponsive to strong stimuli.

At this time the blood pressure was approximately 80 systolic and 42 diastolic. The pulse rate was 108. The respiration was of the Kussmaul type. The eyeballs

TABLE 4.—*Data on the Analyses of the Blood in Case 38 During Severe Diabetic Coma*

Date	Hours	Blood Sugar, Mg. per 100 Cc.	Carbon Dioxide-Combining Power of Venous Plasma Vol. %	Nonprotein Nitrogen, Mg. per 100 Cc.
11/ 8/35	3:30 p.m.	1,068	4	70
	4:30 p.m.	.....	8	..
	5:35 p.m.	1,050	..	..
	7:30 p.m.	690	14	..
	10:30 p.m.	580	19	..
11/ 9/35	7:30 a.m.	110	..	..
11/11/35	7:30 a.m.	50	58	33

TABLE 5.—*Results of Analyses of Urine in Case 38 During Severe Diabetic Coma*

Date, 1935	Volume, Cc.	Sugar, %	Diacetic Acid	Acetone	Ammonia (Calculated as Ammonia), Gm.	Nitrogen, Gm.
Nov. 8, admission specimen.....	240	3.9	0	0	0.14	0.59
Nov. 8 and 9, 15 hour specimen.....	1,350	2.5	0	..	1.16	9.70
Nov. 11 and 12, 24 hour specimen...	1,850	0.4	0	..	3.80	....

were so soft that even three hours later, after 1,500 cc. of physiologic solution of sodium chloride and over 200 units of insulin had been administered, Prof. J. H. Waite could not measure the tension of the eyeballs with a tonometer. The patient's hands and feet were extremely cold. The entire trunk, face, arms and scalp were spotted with superficial crusted lesions and pustules, later diagnosed as varicella. Incidentally, varicella developed in the patient's daughter a few days later. A few râles were heard in the lungs, but later roentgenograms showed no parenchymal involvement. Analyses of the blood and urine, with a summary of the treatment given, are detailed in tables 4 and 5. Treatment consisted of the administration of 220 units of insulin within the first hour and a total of 430 units during the first five hours (see table 6). Physiologic solution of sodium chloride was given subcutaneously and intravenously. Gastric lavage was performed.

The subsequent course in the hospital was entirely uneventful. The patient left the hospital on November 26, on a diet of 171 Gm. of carbohydrate, 114 Gm. of

protein and 121 Gm. of fat, making a total of 2,229 calories. His weight was 135 pounds (61 Kg.), in contrast to 127 pounds (58 Kg.) at the time of his admission to the hospital. The dosage of insulin was 24 units before breakfast, 8 units at noon, 24 units before supper and 8 units at midnight. On this regimen the urine was free from sugar.

The total energy exchange is usually increased in the early stages of diabetic coma. Contributing to this effect are undoubtedly the extra exertion involved in the deep respiration and the restlessness of the patient, as well as the direct effect of the acidosis. This was observed in the cases studied by one of us [14] at the Carnegie Nutrition Laboratory and was also shown in a case of coma (case 36) studied at the Deaconess Hospital shortly before the case under discussion. In this early stage there is no fall in the body temperature. However, as acidosis advances and exhaustion comes on with dehydration, the body temperature falls, and in this stage there may be a change in the total energy exchange.

TABLE 6.—*Treatment in Case 38 During Severe Diabetic Coma*

Hours After Admission	Insulin, Units	Saline Solution	
		Intravenous, Cc.	Subcutaneous, Cc.
1	220	...	1,500
2	40	750	.....
3	40	...	.....
4	90	...	.....
5	40	...	.....
8-11	80	750	1,500

In order to study this point, we were able, through the courtesy of Dr. Francis G. Benedict and Dr. Thorne Carpenter, of the Carnegie Nutrition Laboratory, to observe the oxygen exchange of the aforementioned patient by means of the helmet apparatus devised by Dr. Benedict. With this apparatus no nose clips or mouth piece are necessary, and with a patient thoroughly relaxed in deep coma, no struggling or other complicating factors enter in. The results obtained for the oxygen consumption in this case are shown in table 7.

At 4:45 p. m. on November 8, when the patient was apparently dying and the rectal temperature was low, the oxygen consumption was lower than it was five hours later, when after treatment the rectal temperature had risen. After the patient's recovery from acidosis the basal metabolism fell again to a level of 1,536 calories on November 25. The lower value of oxygen absorption at the height of coma, even though it was still higher than the level obtained later, after complete recovery, tends to support the view that the low body temperature in

14. Joslin, E. P.: Diabetic Metabolism with High and Low Diets, Washington, D. C., Carnegie Institution of Washington, 1923, pp. 158-160.

diabetic coma is not due merely to loss of heat through the evaporation of water but is really due to a depression of heat production, which is directly proportional to the length and severity of the acidosis. However, these are merely preliminary observations, awaiting further study before conclusions can be drawn.

Another evidence of the severity of diabetic coma is the character of the respiration. In the early stages of diabetic coma the respiration may be extraordinarily regular, even though deep. However, when exhaustion sets in and the body temperature falls, the character of the respiration may continue to be deep but may become irregular. In case 38 the tracings of the respiratory rate showed a considerable variation, although this did not interfere with an accurate determination of the oxygen consumption. The rate varied from 35 to 40 a minute. This rate steadily fell and four hours later was 25 per minute.

Renal function is of fundamental importance in the early stages of diabetic acidosis and also later, as it is often the determining factor in

TABLE 7.—*Oxygen Absorption per Minute in Case 38 During and Subsequent to Diabetic Coma*

Date, 1935	Hour	Oxygen Absorbed per Minute, Cc.	Temperature, F.
Nov. 8	4:45 p.m.	286	96.0 (rectal)
Nov. 8	9:45 p.m.	385	99.0 (rectal)
Nov. 9	8:00 p.m.	317	99.0 (rectal)
Nov. 16	8:00 a.m.	300	97.8 (by mouth)
Nov. 25	8:00 a.m.	275	98.0 (by mouth)

recovery. In the foregoing case, a specimen of urine obtained by catheter was free from diacetic acid and acetone. The total amount of ammonia was 0.14 Gm., and in this same specimen the total urinary nitrogen content was 0.59 Gm., making the ammonia nitrogen-total nitrogen ratio 19 per cent. During the next eighteen hours the urine contained only 1.16 Gm. of ammonia, and the total nitrogen content was 9.7 Gm., giving a still lower ammonia nitrogen-total nitrogen ratio of 9.9 per cent. This extraordinarily low rate of ammonia formation indicated a marked impairment of renal function and a marked diminution in the process of ammonia formation within the kidneys.[14a] In some cases of diabetic acidosis Goodall and one of us [15] found ammonia values as high as 5.2 Gm. in twenty-four hours and an ammonia nitrogen-total nitrogen ratio up to 39 per cent. Another evidence of impairment of the renal function is the fact that the nonprotein nitrogen content of the blood

14a. Another interpretation would be that there was sufficient alkali in the body and no necessity to utilize this mechanism.

15. Goodall, H. W., and Joslin, E. P.: The Clinical Value of the Estimation of Ammonia in Diabetes, Boston M. J. **158**:646 (May) 1908.

was 70 mg. per hundred cubic centimeters. Furthermore, it is worth noting that although the specimen of urine contained no diacetic acid or acetone, a qualitative test for acetone performed on the blood plasma showed a maximal amount of acetone present. The concentration of chloride in the urine was at a minimum. The first catheter specimen of urine contained 0.2 Gm. of sodium chloride, or a concentration of 0.08 per cent. This, again, is an index of the degree of dehydration as well as of poor renal function, indicating a late stage of acidosis.

In keeping with these results obtained from the urine, the blood showed a sugar concentration of 1,068 mg. per hundred cubic centimeters. This concentration was rapidly reduced with the use of insulin, the patient receiving about 100 units per hour during the first three hours of treatment and a total of 510 units in the first eleven hours.

For this discussion the most important of the analyses of the blood was that of the carbon dioxide-combining power of the venous plasma.[16] The value obtained was 4 volumes per cent. It should be remembered that the low value of 4 volumes per cent for the carbon dioxide-combining power represents the bicarbonate concentration of the separated plasma equilibrated with 5.5 per cent carbon dioxide (alveolar air) at room temperature. The carbon dioxide content of venous plasma, i. e., the concentration of bicarbonate plus dissolved carbon dioxide, amounted to 8.5 volumes per cent about one hour after the patient's admission to the hospital and after 150 units of insulin had been administered and was determined by Prof. A. B. Hastings. Dr. John Talbot, of the Massachusetts General Hospital, analyzed arterial blood about one and a half hours after the patient's admission to the hospital, when 1,500 cc.

16. The carbon dioxide-combining power of the venous plasma of our patients in coma has been determined under the direction of Miss Hazel Hunt, formerly the private assistant of Prof. Otto Folin, by the method of Van Slyke and Cullen (J. Biol. Chem. **30**:289, 1917), except that the apparatus used has a specially designed pipet with a scale-bearing portion about two and one-half times the length of the standard apparatus. This has enabled us to read low values more accurately. Of our 318 patients in coma, 36 have shown the carbon dioxide-combining power of the plasma as determined by this method to be 5 volumes per cent or less; in fact, 9 have had values as low as 2 volumes per cent. In criticizing values as low as these Hartmann (Hartmann,[2] p. 429, footnote 8) overlooked the fact that when one uses the table of Van Slyke and Cullen (J. Biol. Chem. **30**:344, 1917) to calculate the carbon dioxide-combining power, one automatically makes allowance for physically dissolved carbon dioxide. While this method may not give as accurate an indication of the acid-base balance of the blood as do determinations of the hydrogen ion concentration and of the carbon dioxide content of blood drawn anaerobically, it is convenient and practical for clinical laboratories and "gives results practically as valid as determinations of carbon dioxide on anerobically separated plasma," according to Peters and Van Slyke (Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 251).

of physiologic solution of sodium chloride subcutaneously and 220 units of insulin had been administered. This arterial blood had a carbon dioxide content of 5.3 volumes per cent.

The increase in the carbon dioxide-combining power of the blood was steady so that within seven hours on November 8 the value had risen to 19 volumes per cent. On November 11 the carbon dioxide-combining power of the venous plasma was 58 volumes per cent. The use of sodium lactate in racemic mixture has been suggested.[17] Two articles by Prof. Graham Lusk[18] on the effect of lactic acid on the metabolism give some data on its effect when given to dogs.

Lusk added sodium bicarbonate in certain of his experiments so that he was practically giving sodium lactate to the dog. It is not possible to see from the data which he gave that the addition of sodium bicarbonate, bringing about practically a solution of sodium lactate, made any difference in the results of the metabolic studies. If anything, the sodium lactate gave slightly lower results, but it is questionable whether the differences are significant. Apparently the sodium lactate had no more influence on the metabolic rate of these animals than dextrose would have had.

Hartmann[19] stated that racemic sodium lactate given in amounts equivalent to 7 cc. of molar solution per kilogram of body weight produces an increase of 25 to 50 per cent in the oxygen consumption when injected intravenously in normal human subjects, and he said that a similar effect probably occurs in the diabetic patient. Indeed, he attributed the intense hyperpyrexia in 1 of his cases of fatal diabetic coma to this cause. Therefore he recommends a sixth-molar solution of racemic sodium lactate in amounts equivalent to 1 Gm. of sodium bicarbonate per kilogram of body weight. He maintained that this large amount may safely be given without danger of alkalosis, because the sodium lactate must first be metabolized before it is converted into sodium bicarbonate. Such metabolism requires from two to four hours![20] In a case of advanced coma death might occur before the solution of sodium lactate was metabolized.

Actually the dose amounts to 60 cc. per kilogram of body weight, or 3,600 cc. of sixth-molar concentration for a man weighing 133 pounds (60 Kg.). It would be of value to see the respiratory data for a patient in advanced diabetic coma so treated. We have already obtained the solution, and if we find it of value we will report on it.

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17. Hartmann,[2] p. 434.

18. Atkinson, H. V., and Lusk, G.: The Influence of Lactic Acid upon Metabolism, J. Biol. Chem. **40**:79 (Nov.) 1919. Lusk, G.: The Behavior of Various Intermediary Metabolites upon Heat Production, ibid. **49**:453 (Dec.) 1921.

19. Hartmann,[2] p. 431.

20. Hartmann,[2] p. 430.

DIABETIC COMA IN CHILDHOOD AND YOUTH

Can the treatment of severe diabetic acidosis which is used at present in the St. Louis Children's Hospital be recommended as a safe method for the youthful patient? The mortality among 16 patients so treated was 13 per cent,[21] which was (*a*) six times the mortality among 54 children in diabetic coma whose plasma combining power was 15 volumes per cent or less and who were treated without alkali at the George F. Baker Clinic of the New England Deaconess Hospital between 1923 and December 1935, with 1 death, or a mortality rate of 1.8 per cent; (*b*) thirteen times the mortality for our 87 cases in which the onset of diabetes occurred when the child was less than 15 years old and the plasma carbon dioxide content was 15 volumes per cent or less (a severer test of therapy, for mortality increases with age), in which there was 1 death, or a mortality of 1 per cent; (*c*) twenty times the mortality for our 134 cases, if we adhere to our former classification of coma (fall of the plasma combining power to 20 volumes per cent or below), in which there was 1 death, or a mortality of 0.7 per cent.

It is unfortunate that in 2 of Dr. Hartmann's cases of pneumonia the diagnosis was not proved by roentgenographic or pathologic examination, because the frequent occurrence of fever, leukocytosis and râles during coma throws some doubt on such an unsubstantiated diagnosis. Of our 134 juvenile patients, 10 had râles and a total of 21 had infections, including acute infection of the respiratory tract, acute appendicitis, pyelitis, carbuncles and tuberculous pneumonia; all recovered, although the patient with tuberculosis died eight months later in a state sanatorium for tuberculous patients.

It is true that without alkali the average rise of the alkali reserve is slow—11 volumes per cent in Hartmann's series of 16 cases and 12 in ours eight hours after treatment. But if our comparable mortality rate is only 2 per cent and his with a more rapid rise is six times that, can we believe that the slow rise is harmful? Is it not more logical to believe that the rapid rise gives a false sense of security and that the fundamental fault in diabetes, namely, insulin insufficiency, has been overlooked?

Is the suggestion in Dr. Hartmann's paper substantiated—that diabetic coma because it occurs in Boston is of necessity of lesser degree than that which occurs in St. Louis? Do his chemical and clinical data

21. Hartmann,[2] p. 422, chart 4. Here he mentioned 16 cases, but on comparison with table 1, page 415, it appears that only 12 patients with severe acidosis were treated with the racemic lactate. Evidently he has added 4 cases from the 5 mentioned in the footnote on page 414 with a carbon dioxide content of 9.6, 11.5, 12.2, 21.7 and 26 volumes per cent, respectively, although it seems as though only the first 3 of these were relevant.

bear this out? Actually he has included in his series of 86 cases 14 in which the carbon dioxide content was over 35 volumes per cent—undeniably mild involvement. Even in the 19 cases in which the carbon dioxide content was between 25 and 35 volumes per cent the disorder was too mild to be considered in discussing the treatment of "severe acidosis," although concomitant infection might have made the general clinical condition precarious.

The author is mistaken in the statement [22] that he followed our methods of treatment, as his dosage of insulin was so much less than ours. The range in our series has been from 0.2 to 17 units per kilogram of body weight in twenty-four hours. Usually three fourths of the amount is administered in the first six hours by subcutaneous injection in small divided doses at intervals of from fifteen minutes to one hour. In 8 of our entire series of cases in which from 10 to 17 units per kilogram of body weight had been given, we are afraid that death would have intervened if only 2 units of insulin per kilogram of body weight had been given in the initial dose and none for six hours.

CONCLUSIONS

Three hundred and eighteen patients in diabetic coma with a carbon dioxide-combining power of the venous plasma of 20 volumes per cent or less have been treated without alkalis, with a mortality of 11.9 per cent. Among the last 42 cases there were 3 deaths, giving a mortality of 7.1 per cent. In 1 of these 3 fatal cases insulin was not given because of an error in diagnosis. The second patient died eight days after relief from acidosis was obtained, as a result of infection of the genito-urinary tract. The third patient died twenty days after relief from acidosis was obtained, as a result of infection of the leg. Considering children aged 15 years or less at the time of the coma, there has been only 1 death among 87 patients with an initial carbon dioxide-combining power of the plasma of 20 volumes per cent or less and 1 death (the same patient) among 54 with an initial carbon dioxide-combining power of 15 volumes per cent or less. Until data are reported which show better results than those obtained with our methods, often previously described, we see no reason to adopt more complicated procedures involving the use of alkalis or, specifically, sodium lactate which in the hands of their originators yield results inferior to ours.

No universal rule for the administration of insulin in coma is possible, because insulin must be given according to the severity of the coma, determined clinically and chemically, the age of the patient, the body weight, the duration of the diabetes as well as of the coma and the preceding treatment, particularly with insulin. Believing that one cannot

22. Hartmann,[2] p. 428.

predict the course of diabetic coma for six hours in advance, we disapprove of an endeavor to give a single dose of insulin and no other until the end of that period.

Our results have been secured by the use of (1) insulin given subcutaneously, and at times intravenously, every fifteen to thirty minutes in doses of 20 to 50 units (occasionally as high as 100 units, especially intravenously) amounting in the average case to approximately 200 units in twenty-four hours; (2) the liberal use of salt solution subcutaneously and often intravenously as well to combat dehydration; (3) lavage of the stomach in nearly all instances unless the attending doctor accepts full responsibility for its omission; (4) liquids by mouth at an initial rate not to exceed 100 cc. hourly and (5) unless 50 Gm. of soluble carbohydrate or more is taken in the first twelve hours and again in the second twelve hours, dextrose intravenously or subcutaneously, and (6) always an endeavor to protect and stimulate the circulation by good nursing and by the use of epinephrine and ephedrine for falling blood pressure.

STUDIES OF UROBILINOGEN

II. UROBILINOGEN IN THE URINE AND FECES OF SUBJECTS WITHOUT EVIDENCE OF DISEASE OF THE LIVER OR BILIARY TRACT

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The tests for urobilinogen in the urine and feces which are commonly employed in the clinical study of jaundice and of hepatic function have not met with general approval, because of the varying and indefinite results obtained. In a recent review of the literature on tests of hepatic function by Soffer [1] this was in effect the conclusion reached. When one considers the varying dilution of the urine as well as the varying hourly excretion of the normal traces of urobilinogen in the urine (Bang [2]) and the much larger amounts present in the normal feces (Singer [3]), in which the concentration also is subject to wide variation, and when one considers further the daily and even hourly variations in the degree of urobilinuria in pathologic states, it is little wonder that qualitative tests, such as those of Ehrlich [4] and Schlesinger,[5] and roughly quantitative procedures, such as those of Wilbur and Addis [6] and Wallace and Diamond,[7] have often yielded confusing results. The need for knowledge of the per diem excretion of urobilinogen has been recognized by many, among whom von Müller [8] and Gerhardt [9] were

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1. Soffer, L. J.: Present Day Status of Liver Function Tests, Medicine **14**:185, 1935.

2. Bang, O.: Klinische Urobilinstudien in Sonderheit an normalen und "lebergessunden" Personen: Die Wirkung kohlehydratknapper Kost auf die Urobilinausscheidung; die Urobilinurie der Diabetiker, Acta med. Scandinav., supp. 29, 1929, p. 1.

3. Singer, K.: Studien zum Problem der Blutmauserung: Ueber den Einfluss der Ernährung auf die Urobilinogenausscheidung mit dem Fäzes, Wien. Arch. f. inn. Med. **20**:59, 1930.

4. Ehrlich, P.: Ueber die Dimethylamidobenzaldehydereaktion, Deutsche med. Wchnschr. **27**:151, 1901.

5. Schlesinger, W.: Zur klinische Nachweis des Urobilins, Deutsche med. Wchnschr. **29**:561, 1903.

6. Wilbur, R. L., and Addis, T.: Urobilin: Its Clinical Significance, Arch. Int. Med. **13**:235 (Feb.) 1914.

7. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:689 (June) 1925.

8. von Müller, F.: Ueber Ikterus, Jahresb. d. schles. Gesellsch. f. vaterl. Cult. (Med. Sekt.) **70**:1, 1893.

9. Gerhardt, D.: Ueber Urobilin, Ztschr. f. klin. Med. **32**:303, 1897.

the earliest. Eppinger and Charnas [10] and later Eppinger [11] made a considerable advance in the study of this subject. Employing more reliable methods, Lichtenstein and Terwen,[12] Adler and Bressel [13] and I [14] further demonstrated the potential value of estimation of urobilinogen. As yet, however, there has been no systematic investigation of the daily excretion of urobilinogen in the various types of jaundice and hepatic disease. By this is meant that the number of instances of any one disease has been too small in previous studies to permit of urobilinogen estimations in the study of this group of diseases.

In a separate communication [15] reasons were given for distrusting the methods depending on the characteristics of urobilin, and an improved method for the quantitative estimation of urobilinogen was described. This method has been used in a study of the urobilinogen excretion of two hundred and five subjects. The present communication deals with the excretion of urobilinogen by normal subjects and by subjects suffering from various abnormal states, such as fever, malnutrition, inactivity, anemia and hematopoietic disease, in all of which jaundice or hepatic disease, if present, was not the primary or prominent pathologic process. This investigation is introductory and particularly intended to serve as a control for that reported in paper III of this series, which will follow. In paper III the excretion of urobilinogen in one hundred and thirty-five cases of the common forms of jaundice and hepatic disease will be discussed, and it will be shown that the various forms of jaundice are rather uniformly characterized by per diem excretion of urobilinogen of different magnitudes, which has evidently not been emphasized sufficiently in the past. This is particularly true for the distinction of obstructive jaundice due to neoplastic disease from other forms of jaundice. It has been found that a heightened excretion of urobilinogen in the urine, when studied with the method described, is an almost constant accompaniment of hepatic dysfunction or diffuse hepatic disease. In a later communication a com-

10. Eppinger, H., and Charnas, D.: Was lehren uns quantitativen Urobilin Bestimmung im Stuhl? Ztschr. f. klin. Med. **78**:387, 1913.

11. Eppinger, H.: Die hepatolienalen Erkrankungen, Berlin, Julius Springer, 1920, pp. 76-91.

12. Lichtenstein, A., and Terwen, A. J. L.: Ueber Blutmauserung und Urobilinausscheidung, Deutsches Arch. f. klin. Med. **149**:113, 1925.

13. Adler, A., and Bressel, M.: Urobilinogenbestimmung in Stuhl und Harnmittels der neuen Extraktionsmethode, Deutsches Arch. f. klin. Med. **155**:326, 1928.

14. Watson, C. J.: The Average Daily Elimination of Urobilinogen in Health and in Disease, with Special Reference to Pernicious Anemia, Arch. Int. Med. **47**:698 (May) 1931.

15. Watson, C. J.: Concerning Urobilinogen: I. An Improved Method for the Approximate Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458, 1936.

parative study of urobilinogen excretion, bromsulfalein retention and galactose tolerance in hepatic disease will be described. From this study it appears that, of the three tests, the determination of the daily amounts of urobilinogen in the urine and feces provides the most reliable information regarding the function of the liver and the causes of jaundice.

MATERIAL AND METHODS

The quantitative method employed in this investigation has been described in detail in paper I of this series [15]; the most important features of the method are given briefly in the following paragraphs:

1. Feces. A 10 Gm. portion of the well mixed collection of feces for a four day period is thoroughly ground in a mortar with a few cubic centimeters of distilled water and diluted further to a total of 300 cc. or only to 100 cc. in case the feces are obviously acholic. This mixture is poured into a 500 cc. Erlenmeyer flask containing 100 cc. of a 20 per cent solution of ferrous sulfate (20 Gm. of ferrous sulfate; 92 cc. of water). Prior to solution the ferrous sulfate is powdered in a mortar. Finally, 100 cc. of a 10 per cent solution of sodium hydroxide is added with constant mixing. The flask is corked and allowed to stand for one hour.[16] To 2 or 3 cc. of the filtrate an equal amount of a modified Ehrlich's reagent [17] is added, and then several cubic centimeters of a saturated aqueous solution of sodium acetate. Depending on the intensity of the color that develops, from 1 to 50 cc. of the filtrate is used in the quantitative procedure. Thus, if the color is intense, 1 cc. or even less will suffice; if pale red, from 5 to 10 cc.; if faint, 25 cc.; if absent, 50 cc. It is desirable that the amount of filtrate chosen should be only enough so that the final colored solution does not exceed 100 cc. and that its color is not more than 50 per cent on the standard scale to be described. The amount of filtrate decided on is placed in a 125 cc. pear-shaped separatory funnel, covered with 30 cc. of purified petroleum benzine (petroleum ether)—after the filtrate is diluted to 20 cc. with distilled water if less than this amount of filtrate was used—and then strongly acidified with glacial acetic acid and shaken vigorously for several seconds. After separation the aqueous fraction is extracted twice more with purified petroleum benzine. The combined solution of petroleum benzine is washed twice with water and then shaken vigorously with 1 or 2 cc. of the modified Ehrlich reagent. At least twice as much of a saturated aqueous solution of sodium acetate is added, the maximum color now appearing. After vigorous shaking the colored solution is separated into a 100 cc. graduated cylinder, and the petroleum benzine is again extracted with Ehrlich's reagent. This is repeated until the urobilinogen has been entirely removed (there is no further development of color). Each extraction is followed by the addition of sodium acetate, shaking and separation of the aqueous fraction into the cylinder. The colored solution is then made up to a volume convenient for calculation and mixed, and a sufficient amount is poured out to

16. Slightly lower values are obtained if the mixture is allowed to stand over night. For this reason the values given subsequently, as well as in part III, are undoubtedly slightly too low, since the mixture was allowed to stand over night in most of these instances.

17. This contains 0.7 Gm. of paradimethylaminobenzaldehyde, 150 cc. of concentrated hydrochloric acid and 100 cc. of distilled water.

fill the right hand test tube of a Hellige-Dunning colorimeter.[18] Should the intensity of color be greater than 50 per cent of the standard, a further dilution is made, as comparisons are most accurate between 20 and 50 per cent.

Calculation:

$$\frac{\text{Cc. of ferrous hydroxide mixture}}{\text{Gm. of feces}} \times \frac{\text{Cc. of final colored solution}}{\text{Cc. of filtrate used}} \times \text{percentage of color standard} \times \frac{\text{weight of 4 day amount of feces}}{100} \times \frac{1}{\text{No. of days' collection of feces}} = \text{Mg. of urobilinogen per day}$$

Example:

$$\frac{500}{10} \times \frac{45}{3} \times 0.35 \times 2.8 \times \tfrac{1}{4} = 183.7 \text{ mg. per day.}$$

Standardization of the colorimeter in terms of crystalline mesobilirubinogen (urobilinogen) has been described in the publication already referred to.[15]

2. Urine. A twenty-four-hour sample of urine is collected in a dark bottle containing approximately 5 Gm. of sodium carbonate and 100 cc. of purified petroleum benzine.[19] After collection the urine is separated from the petroleum benzine and measured. Fifty cubic centimeters of the mixed urine is placed in an Erlenmeyer flask of 300 or 500 cc. capacity. To this is added, with thorough mixing, 25 cc. of 20 per cent ferrous sulfate (5 Gm. of the powdered crystals of ferrous sulfate dissolved in 23 cc. of water) and 25 cc. of 10 per cent sodium hydroxide. After one hour a qualitative test on the filtrate determines the optimal amount for the quantitative procedure. The amount chosen is treated in the same way as given previously for the feces. The extraction of urobilinogen from the petroleum benzine is carried out in the manner given for the feces. A comparison is then made in the colorimeter. The calculation is as follows:

$$\frac{100}{50} \times \frac{\text{Cc. of final colored solution}}{\text{Cc. of filtrate used}} \times \text{Percentage of standard} \times \frac{\text{Vol. of 24 hour urine}}{100} = \text{Mg. of urobilinogen in 24 hours}$$

Example (hepatic dysfunction):

$$\frac{2}{2} \times 20 \times 0.18 \times 14 = 50.4 \text{ mg. in 24 hours.}$$

18. A permanent glass standard colorimeter for determinations of phenolsulphonphthalein in urine obtained from Hynson, Westcott and Dunning Co., Baltimore.

19. In paper I results of comparative estimations following different methods of collecting the urine were given. The majority of the results which are given here and in paper III were obtained after collection of the urine in ferrous hydroxide. It was shown in paper I that the collection under petroleum benzine is somewhat more efficient; for this reason the values to be given here and in part III are slightly low.

Case	Diagnosis	Sex	Age	Hemoglobin, %	Icterus Index	Urobilinogen Excretion, Mg. per Day: Urine	Urobilinogen Excretion, Mg. per Day: Feces
Group 1. Normal Subjects and Hospital Patients Without Fever, Anemia, Jaundice or Other Evidence of Disease of the Liver or Biliary Tract							
	A. Feces and Urine						
1	Normal	M	25	85	..	Trace	156.4 189.0
2	Normal	M	29	89	..	0.93	108.0
3	Normal	M	24	102	..	2.16	279.4
4	Normal	F	22	85	..	0.46 2 mo. later	40.9 42.0
5	Normal	M	55	90	..	....	162.0
6	Normal	F	21	85	..	Trace	180.2
7	Normal	M	40	98	..	Negative	261.2
8	Normal	M	34	90	..	0.40	278.4
9	Normal	M	23	85	..	3.60	199.8
10	Normal	M	19	96	..	Trace	140.4
11	Normal	M	24	..	..	1.70	259.9
12	Normal	M	25	87	..	3.40	89.8
13	Normal	M	26	101	..	0.35	158.3
14	Normal	M	24	..	..	....	189.0
15	Normal	F	22	82	..	0.80	76.0
16	Epilepsy	M	33	101	..	0.50	262.5
17	Spinal cord tumor (no paralysis)	M	52	97	..	0.70	201.2
	B. Additional Determinations						
18	Normal	F	22	..	..	0.98	.....
19	Normal	F	20	..	..	1.20	.....
20	Normal	F	22	..	..	1.70	.....
21	Normal	M	25	..	..	2.00	.....
22	Fracture of femur	M	40	..	..	1.10	.....
23	Quiescent tuberculosis of spine	F	42	..	..	Trace	.....
24	Obesity (397 pounds)	M	46	..	..	0.70	.....
25	Injury to eye	M	46	..	..	1.80	.....
26	Gastric ulcer	M	32	..	..	Trace	.....
Group 2. Persons with Mild Infection, Inanition or Inactivity (No Jaundice or Anemia)							
27	Atrophy of optic nerve; sciatic neuritis	M	37	91	..	Trace	54.2
28	Chronic arthritis	M	31	81	..	1.00	93.8
29	Multiple neuritis	F	38	90	..	0.24	22.8
30	Inanition following burns; pyelonephritis; nephrolithiasis	F	17	82	..	Negative	38.6 25.1
31	Large carcinoid tumor of cecum; extreme inanition	F	63	77	..	....	8.8
Group 3. Persons with Conditions Associated with Fever							
32	Subacute bacterial endocarditis; constant fever, 100 to 103 F.	M	45	63	14	Trace	.....
33	Subacute bacterial endocarditis; continuous fever, 101 to 103 F.; 26,000 leukocytes	M	17	52	28	0.85	.....
34	Undulant fever; temperature 99 to 101 F.; no jaundice	F	24	74	..	0.80	.....
35	Infectious arthritis; fever, 99 to 102 F.; no jaundice	F	42	57	..	Negative	.....
36	Hodgkin's disease with fever, anemia, splenomegaly	M	34	36	..	....	225.8
37	Hodgkin's disease; intermittent fever; splenomegaly; anemia	M	35				
	Febrile	..	..	51	18	35.3	269.8
	Afebrile	..	..	50	12	....	127.4
38	Malaria (therapeutic)	M	31	76	10	10.9	233.9
39	Pneumonia following postoperative atelectasis; mild icterus	M	38	89	26	37.6	.....
40	Pelvic cellulitis and bacteremia; jaundice	F	38	70	27	20.5	208.2
41	Pulmonary abscess; empyema; no jaundice	M	37	55	..	8.3	.....
42	Lobar pneumonia; slight icterus	F	22	86	20	32.5	325.5

Data on the Urinary Excretion of Urobilinogen—Continued

Case	Diagnosis	Sex	Age	Hemoglobin, %	Icterus Index	Urobilinogen Excretion, Mg. per Day: Urine	Urobilinogen Excretion, Mg. per Day: Feces
	Group 4. Persons with Anemia or Other Hematopoietic Disease						
43	Pernicious anemia	F	44				
	Prior to liver therapy	..	..	20	27	6.70	587.0
	After liver therapy	..	..	44	11	0.30	210.0
44	Pernicious anemia	F	40				
	Prior to liver therapy	..	..	28	22	0.70	600.0
	After liver therapy	..	..	65	..	....	189.3
45	Pernicious anemia	M	52				
	Prior to liver therapy	..	..	15	11	16.10	338.0
	After liver therapy	..	..	53	..	0.20	61.0
46	Pernicious anemia, prior to liver therapy	M	25	44	..	2.90	622.5
47	"Pernicious" type of anemia with pregnancy; free hydrochloric acid in gastric contents	..	..	24	16	1.90	330.2
48	Hyperchromic anemia with myxedema; 2,480,000 erythrocytes	F	51	65	10	Trace	22.5
							46.3
							66.1
				49	..	....	25.2
				67	..	....	126.7
49	Hyperchromic anemia with lymphatic leukemia; leukopenia with many immature lymphocytes; no enlargement of spleen, liver or lymph nodes	F	38	60	..	....	27.0
50	Hypochromic anemia due to bleeding hemorrhoids	F	39	51	13	0	71.9
51	Idiopathic hypochromic anemia; dysphagia; koilonychia; hypochlorhydria	F	43	54	..	Trace	53.8
				56	..	....	53.3
52	Idiopathic hypochromic anemia; achlorhydria	F	47	40	6	0	45.4
53	Idiopathic hypochromic anemia; menorrhagia; glossitis; dysphagia; marked koilonychia; free hydrochloric acid	F	40	44	..	Trace	21.0
54	Idiopathic steatorrhea (nontropical sprue); Hypochromic anemia	M	42	66	4.5	4.50	127.5
55	Hypochromic anemia of pregnancy	F	19	44	5.0	Trace	107.0
56	Severe anemia following pregnancy; no response to liver therapy; improvement following transfusions	F	29	13	10.0	....	24.0
57	Skin tuberculosis; Little's disease; mild hypochromic anemia	M	18	76	..	0.40	34.4
58	Mild hypochromic anemia	F	18	74	..	Trace	41.6
59	Osteomyelitis; hypochromic anemia; low grade fever	F	54	60	..	Negative	16.5
60	Probable Banti's disease; 8 months' pregnancy; hypochromic anemia	F	24	53	6	20.70	121.9
	16 months later, spleen remains markedly enlarged	..	..	78	..	1.60	210.6
61	Hypochromic anemia with multiple bone metastases from carcinoma of breast	F	43	25	6	....	56.0
62	Myelophthisic anemia with aleukemic lymphadenosis	M	53	34	9	1.40	6.5
63	Lead poisoning; colic; basophilic stippling	M	50	60	..	....	173.4
64	Polycythaemia vera; large subcutaneous hematoma in flank and loin appeared several days before admission; 7,400,000 erythrocytes	M	61	129	11	2.10	491.0
						9.80	431.7
	Two months after disappearance of hematoma	..	..	114	14	3.30	191.6
65	Polycythaemia vera; 7,800,000 erythrocytes	M	60	106	..	....	104.1
66	Polycythaemia vera (3 years); angina pectoris; recent congestive heart failure; 5,850,000 erythrocytes	M	53	122	..	1.70	344.7
67	Polycythaemia vera; 7,750,000 erythrocytes	M	53	134	27	Trace	110.6
					26		
68	Polycythaemia vera; 6,700,000 erythrocytes	F	57	118	17	Trace	347.6
69	Polycythaemia vera; 5,950,000 erythrocytes	M	69	124	7	Negative	37.8

Throughout this investigation, as well as that which is reported in paper III, specimens of urine giving a negative or low value with the quantitative method were subjected to the ordinary qualitative tests of Ehrlich and Schlesinger. In a few instances only, one or the other or both of these tests were found to be weakly or questionably positive. However, a weak Ehrlich reaction is not necessarily indicative of the presence of urobilinogen. In certain instances it was found that the petroleum benzine extract of urine which exhibited a weak Ehrlich reaction did not show the characteristics of urobilin, i. e., absorption at 495 millimicrons and green fluorescence with zinc after prolonged exposure to light, nor did these characteristics appear after application of the Garrod-Hopkins [20] precipitation with ammonium sulfate followed by exposure to light. On one occasion the Ehrlich reacting substance, after acidification of the filtrate, was not extracted by petroleum benzine, and in this instance the absorption spectrum of the urine with Ehrlich's reagent was not that of the urobilinogen-aldehyde compound. The maximum absorption of the former was found to be at 574.6 millimicrons, and weaker absorption was noted at 534.7 millimicrons, while a urobilinogen-aldehyde solution exhibited absorption at a maximum of 561.1 millimicrons. On superimposition of these spectra, a wide separation of the bands was observed. This substance could not be identified, but it did not appear to be indole or skatole, since it was not extracted with petroleum benzine and since the Ehrlich reaction did not disappear after the addition of sodium acetate.[21]

The studies composing paper I include estimations of the excretion of urobilinogen in sixty-nine instances. These have been divided into four groups as follows:

	No. of Subjects
Group 1. Normal subjects and hospital patients not having fever, anemia, jaundice or any evidence of disease of the liver or of the biliary tract	
A. For whom both urine and feces were investigated	17
B. For whom only urine was investigated	9
Group 2. Subjects in whom mild infection, inanition or inactivity was the only abnormal factor present	5
Group 3. Hospital patients having various febrile diseases	11
Group 4. Patients with anemia, leukemia, polycythemia or some other hematopoietic disease	27

The percentage of hemoglobin was estimated by the Sahli method, 17 Gm. of hemoglobin per hundred cubic centimeters corresponding to 100 per cent. The icturus index was determined by Bernheim's [22] modification of Meulengracht's method.

20. Garrod, A. E., and Hopkins, F. G.: On Urobilin: I. The Unity of Urobilin, J. Physiol. **20**:112, 1896.

21. Terwen, A. J. L.: Ueber eine neues Verfahren zur quantitativen Urobilinbestimmung im Harn und Stuhl, Deutsches Arch. f. klin. Med. **149**:72, 1925.

22. Bernheim, A. R.: The Icterus Index (a Quantitative Estimation of Bilirubinemia): An Aid in Diagnosis and Prognosis, J. A. M. A. **82**:291 (Jan. 26) 1924.

COMMENT ON OBSERVATIONS

The results noted in the accompanying table indicate that the urinary urobilinogen, as determined by the method described, varies normally between 0 and 4 mg. per day, usually from 0.5 to 2 mg. In the earlier investigation already referred to [14] the urobilinogen content of the feces in thirteen normal subjects varied between 54 and 245 mg. per day. The values noted in the present investigation indicate a range from 40 to 280 mg.; so it is evident that there is rather wide variation in the normal excretion of urobilinogen in the feces. Inactivity, inanition or low grade infection or a combination of these appears to be accompanied with a decrease in the amount excreted.

The values in group 3 demonstrate that fever alone is insufficient to cause increased excretion of urobilinogen in the urine. Weiss [23] has emphasized this fact by stating that urobilinuria and fever are not coordinated phenomena. The type of infection appears to be a more important factor. Urobilinuria in pneumonia has been emphasized by Weiss,[23] Adler and Bressel [13] and Simpson,[24] and the latter author was one of the first to stress its occurrence in malaria. Weiss [23] stated that febrile conditions are often associated with an increased excretion of urobilin in the feces. The present results appear to bear out this statement, although in only two instances were the amounts sufficiently high to be decisive. The first (case 42) was an instance of lobar pneumonia with icterus, and the second (case 37), one of Hodgkin's disease during a febrile period. In neither could the icterus be said to have been more than partly hemolytic in origin, since the large amount of urobilinogen in the urine pointed to a considerable reduction in the hepatic function. It is worthy of note that in the instance of Hodgkin's disease mentioned the output of urobilinogen was more than halved after the fever abated. The possible relationship of fever, anemia and an increased destruction of blood in Hodgkin's disease, as measured by the excretion of urobilinogen, is deserving of further study. An instance of profound hemolytic anemia in a patient with Hodgkin's disease and persistent fever has recently been observed; the findings will be presented in paper III of this investigation in the section devoted to hemolytic jaundice.

Unfortunately, it is difficult, and at times impossible, to obtain satisfactory collections of stools from persons suffering from severe febrile disease. In several of the cases in group 3 attempts were made to obtain four day collections of feces, but the amounts were so small that no

23. Weiss, M.: Ueber Urobilin und seine diagnostische Verwertung, Wien. Arch. f. inn. Med. **20**:39, 1930.

24. Simpson, G. C. E.: On the Quantitative Estimation of Urobilin in the Excreta, and Its Value as a Measure of Haemoglobin Metabolism, Biochem. J. **6**:378, 1911.

reliance could have been placed on determinations based on them. Since in normal subjects a four day collection of feces weighs between 300 and 500 Gm., estimations based on collections weighing less than 250 Gm. must be expected to yield relatively lower values. Assuming that none of the feces for the period are lost, this is probably because of an increased resorption of urobilinogen incident to constipation (Wilbur and Addis [6]).

The results in the cases of pernicious anemia are entirely comparable with those which I have previously reported.[14] The marked drop in the amount of urinary urobilinogen coincident with the reticulocyte response to liver therapy was again noted, as was also the considerable decrease in the amount of urobilinogen in the feces. It is noteworthy that in two instances (cases 44 and 46) a considerable increase of urobilinogen was observed in the feces without an increase in the urine. The question of the relationship of urobilinuria to an increased destruction of blood and simple "overflow" of urobilinogen into the general circulation will be discussed in paper III of this series. With the exception of one patient who had a pernicious type of anemia with pregnancy, the other cases of anemia investigated were characterized by normal or less than normal amounts of urobilinogen in the feces. The findings in cases 48 and 49 are particularly significant, since they indicate that hyperchromic anemia need not be accompanied with an increased urobilinogen excretion. Two patients with leukemia, not included among those just mentioned, are of interest in this connection. Both of these patients exhibited a pernicious type of anemia with slight icterus; for one (aleukemic lymphadenosis was proved at necropsy) the amount of urobilinogen excreted in the feces was 350 mg. per day, while the second patient, who had lymphatic leukemia, excreted 1,005 mg. per day during the period studied. This supports the belief that leukemia may be accompanied with an increased destruction of blood. As a result of histologic studies Jaffé [25] stated that he believed that this is the most important factor in the development of leukemic anemia.

In three of the six instances of polycythaemia vera a definite although only moderate increase of the urobilinogen content of the stools was noted (cases 64, 66 and 68). In the first of these, however, the local formation of bilirubin in a large hematoma may have been responsible for the increased amount of urobilinogen in the feces. Some months after the disappearance of the hematoma, the excretion of urobilinogen in the feces had returned to a normal level. Eppinger [10] gave values for four patients with polycythaemia vera; in two of these the output of urobilinogen in the feces was slightly increased and in the other two normal.

25. Jaffé, R. H.: Erythropoiesis, Folia haemat. **49**:51, 1933.

CONCLUSIONS

The amount of urobilinogen excreted in the urine in twenty-four hours by the normal adult varies between 0 and 4 mg., usually being from 0.5 to 2 mg. The normal range for the feces is between 40 and 280 mg. per day, usually from 100 to 250 mg.

Inanition, inactivity or a low grade infection tends to lower the excretion of urobilinogen in the feces; fever of any considerable degree probably tends to increase the amount. Fever alone does not cause an increase in the excretion of urobilinogen in the urine; this is evidently dependent on the type and severity of the infection.

In addition to the various forms of hemolytic jaundice, which will be discussed subsequently, increases of the excretion of urobilinogen were again noted in the feces in cases of pernicious anemia and in instances of Hodgkin's disease and of leukemia. Low values were encountered in certain cases of secondary hyperchromic anemia and in all the cases of hypochromic anemia investigated. Slight increases were observed in half the cases of polycythaemia vera.

STUDIES OF UROBILINOGEN

III. THE PER DIEM EXCRETION OF UROBILINOGEN IN THE COMMON FORMS OF JAUNDICE AND DISEASE OF THE LIVER

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In earlier communications [1] reference was made to the necessity of determining the daily amounts of urobilinogen in the feces and urine rather than attempting to interpret results obtained with qualitative tests. A method for the approximate quantitative estimation of the urobilinogen content was described, and in part II of this series of papers results were given which may be used as controls for the series to be presented here. The former group included normal persons, patients with mild infection, inanition, fever of various cause and anemia and hematopoietic disease of various types. The present investigation deals with the excretion of urobilinogen in the common forms of jaundice and hepatic disease.

MATERIALS AND METHODS

One hundred and thirty-five patients [2] with jaundice or hepatic disease were studied with regard to the per diem excretion of urobilinogen. Their cases may be divided conveniently into seven groups, as follows:

1. Cholecystitis and cholelithiasis	No. of Cases
A. With obstructive jaundice of variable degree but without complications such as severe infection, anemia or cirrhosis secondary to long-standing biliary obstruction (in the majority of these cases clinical or operative evidence of a stone in the common duct was obtained).....	21
B. With complications of the foregoing type.....	20

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1. Watson, C. J.: (*a*) The Average Daily Elimination of Urobilinogen in Health and in Disease, with Special Reference to Pernicious Anemia, Arch. Int. Med. **47**:698 (May) 1931; (*b*) Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458, 1936; (*c*) Studies of Urobilinogen: II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, Arch. Int. Med., this issue, p. 196.

2. Several of these patients were observed in the medical service at the Minneapolis General Hospital. Permission to study these patients was given by Dr. George E. Fahr and Dr. Nathaniel H. Lufkin.

2. Obstructive jaundice due to neoplastic disease of the biliary tract	18
3. Diffuse hepatic disease	
A. Cirrhosis of the liver with considerable jaundice	10
B. Cirrhosis of the liver with jaundice and evidence of increased destruction of blood	7
C. Cirrhosis of the liver with slight or no jaundice	8
D. Acute catarrhal jaundice	11
4. Congestive heart failure with jaundice, enlargement of the liver or ascites	11
5. Carcinoma of the liver or peritoneum with or without ascites and without jaundice	10
6. Miscellaneous hepatic diseases of secondary nature	6
7. Hemolytic jaundice	
A. Familial or congenital	10
B. Acquired	3

The twenty-four hour amount of urobilinogen in the urine was estimated according to the improved method described previously.[3] The per diem excretion of urobilinogen in the feces over a four day period was determined by the same method in the majority of instances, particularly if there was any question as to the degree of biliary obstruction or the rate of destruction of the blood. It was at times impossible to obtain satisfactory collections of feces from very sick patients, especially those with marked congestive heart failure or severe febrile disease. In a few instances only qualitative tests for urobilin and urobilinogen were carried out. For this purpose 1 or 2 Gm. of feces was ground with 5 or 10 cc. of a saturated alcoholic solution of zinc acetate. The filtrate was examined for green fluorescence in front of a point lamp and was then tested for urobilinogen by the addition of 2 or 3 cc. of the modified Ehrlich reagent [1b] followed by 3 or 4 cc. of a saturated solution of sodium acetate. Depending on whether weak, moderate or strong, the intensity of these qualitative reactions is recorded as +, ++ or +++.

The icterus index was determined according to Meulengracht's method (Bernheim's modification[4]). Blood for this determination was obtained while the patient was fasting. The qualitative van den Bergh reaction was carried out in duplicate, with fifteen minutes between the two reactions. The developing color of the second reaction was compared with the fully developed color of the first, the approximate percentage appearing within and after the first minute being noted. Reactions were recorded as follows: (1) direct prompt (all the color developing within one minute), (2) biphasic prompt (more than 50 per cent of the color developing within one minute), (3) biphasic delayed (more than 50 per cent of the color developing after one minute) and (4) delayed (all the color developing after one minute). If none of these appeared, the serum was examined for an indirect reaction after treatment with alcohol in the usual manner.

The percentage of hemoglobin was determined by the Sahli method. Seventeen grams of hemoglobin per hundred cubic centimeters was equivalent to 100 per cent with the apparatus used.

3. Watson.[1a, b]

4. Bernheim, A. R.: The Icterus Index (a Quantitative Estimation of Bilirubinemia): An Aid in Diagnosis and Prognosis, J. A. M. A. **82**:291 (Jan. 26) 1924.

TABLE 1.—*Data on the Excretion of Urobilinogen*

Group 1. Cholecystitis and Cholelithiasis

A. With Obstructive Jaundice of Variable Degree but Without Complications Such as Severe Infection, Anemia or Cirrhosis Secondary to Long Standing Biliary Obstruction (in the Majority of These Cases Clinical or Operative Evidence of Stone in Common Duct Was Obtained)

Case	Condition	Sex	Age	Operation or Autopsy	Icterus Index	Van den Bergh Reaction	Urobilinogen Excretion, Mg. per Day	
							Urine	Feces
1	Gallstone colic; receding jaundice	M	72	..	16	Biphasic delayed	0.90	+++
2	Gallstone colic; recent slight jaundice	F	44	Operation	16	Biphasic delayed	2.10	125.00
3	Gallstone colic; jaundice, 1 week	M	53	Operation	20	.....	4.90	317.20
4	Gallstone colic; jaundice, 3 weeks	F	23	Operation	64	Biphasic delayed	2.20	++
5	Previous cholecystectomy; stones in common duct	F	44	Operation	21	.....	0.80	
6	Repeated colic; mild jaundice	F	53	Operation	15	Delayed	0.20	
7	Painless jaundice, 1 week	F	65	Operation	..	.....	Trace	50.00
	Eight days later, jaundice now of 2 weeks' duration	..	..				0	10.60
8	Repeated colic; recent jaundice	M	60	..	32	.....	1.60	+++
9	Repeated colic; intermittent jaundice	F	56	..	29	Biphasic prompt	0.80	
10	Repeated colic; intermittent jaundice	F	43	Operation	96	.....	4.00	148.00
11	Repeated colic; jaundice, 1 month	F	32	Operation	41	Biphasic delayed	3.50	83.20
12	Previous cholecystectomy; stricture of common duct	M	30	Operation	14	.....	0	
13	Repeated colic; intermittent jaundice	F	49	Operation	85	.....	Trace	++
14	Repeated colic; slight jaundice	M	59	..	21	Biphasic delayed	Trace	
15	Repeated colic; intermittent jaundice	F	63	Operation	12	.....	0	
16	Repeated colic; previous jaundice	F	..	Operation	10	.....	2.20	
17	Slight icterus; pain in right upper quadrant of abdomen	M	71	..	18	Delayed	3.50	
18	Colic in right upper quadrant of abdomen; jaundice, two weeks	F	26	..	66	Biphasic delayed	6.20	37.10
19	Repeated colic; intermittent jaundice	F	40	Operation	26	Biphasic delayed	2.10	225.00
20	Repeated colic; recent jaundice	F	56	Operation	30	Biphasic	0	67.50
21	Reapeated colic; previous jaundice	F	74	..	17	Biphasic	2.80	25.40

B. With Obstructive Jaundice and with Different Complications, Such as Severe Infection, Particularly of the Biliary Tract, or Cirrhosis Secondary to Long Standing Biliary Obstruction

22	Acute cholecystitis; cholangeitis; common duct stone	F	49	Operation	60	.....	10.90	170.20
23	Subphrenic hematoma and abscess following cholecystectomy; sandlike concretions in hepatic duct; severe anemia	F	32	Autopsy	38	Biphasic delayed	37.90	
24	Long-standing recurrent cholangeitis with common duct stone; daily temperature, 104 or 105 F.; chills; increasing jaundice; acute and chronic inflammation in portal spaces of liver with biliary cirrhosis	F	51	Autopsy	52	Biphasic delayed	53.50	246.80
25	Acute cholecystitis	F	63	Operation	19	.....	6.90	
26	Continuous jaundice for 2 years following cholecystectomy; large liver; common duct stricture; biliary cirrhosis	F	44	Autopsy	65	.....	3.90	6.70
27	Acute cholecystitis	F	58	.....	16	Delayed	8.00	
28	Continuous jaundice for 6 months; large liver, finely nodular at operation (biliary cirrhosis); large impacted stone removed from common duct; recovery	F	64	Operation	64	Biphasic prompt	26.20	10.00

29	Frequently recurring jaundice for 2 years; pain in right upper quadrant of abdomen; roentgen evidence of duodenal ulcer or adhesions; large liver; ascites; spontaneous improvement with disappearance of ascites and jaundice...	M	59	.....	32	Biphasic prompt	13.50	
30	Acute cholecystitis, during attack	F	25	Operation	9	.....	20.80	
	Several days after subsidence of acute symptoms	..	..	.....	..	.....	0.18	
31	Frequent gallstone colic with jaundice for 21 years; continuous jaundice for last 12 years; very large liver, finely roughened at operation (biliary cirrhosis)	M	49	Operation	48	Biphasic prompt	25.60	116.00
32	Previous gallstone colic and empyema of gallbladder; deep jaundice for 6 weeks; recovery	F	27	Operation	208	Biphasic prompt	10.80	14.70
33	Previous gallstone colic with frequent jaundice; present jaundice of 6 weeks' duration; large liver, finely granular at operation; recovery	F	50	Operation	48	Biphasic prompt	17.70	14.10
34	Previous attacks of pain in right upper quadrant of abdomen for past 4 years; present attack of 2 weeks' duration with slight jaundice; low grade fever; leukocytes 16,700; evidence of heart failure; dyspnea on exertion; edema of ankles; large, tender liver; right hydrothorax	F	66	.....	31	Biphasic	102.30	
	After 24 hour interval	..	..	.....	..	.....	58.00	
35	Repeated attacks of colic in right upper quadrant for past year; marked jaundice; frequent pain of 3 weeks' duration; fever and leukocytosis; enlargement of liver	F	58	Operation	54	Biphasic prompt	23.40	
	Four days later: jaundice disappearing; no pain or tenderness remaining	..	..	.....	29	.....	2.30	336.10
36	Painless jaundice of 3 months' duration; large stones removed from common duct at operation; early biliary cirrhosis noted	F	..	Operation	59	Biphasic delayed	8.30	21.80
37	Previous colic in right upper quadrant of abdomen, with jaundice; chills and fever (105 F.) with present attack; deep jaundice	F	37	Operation	92	Prompt	4.20	12.80
	Marked improvement	..	..	.....	38	.....	47.50	621.60
	Jaundice subsiding	..	..	.....	19	.....	.....	165.00
	Operation: stone in dilated common duct	..	..	.....	24	.....	2.30	100.20
38	Repeated gallstone colic; present attack with jaundice, fever, pain and tenderness in right upper quadrant of abdomen; leukocytosis	M	55	Operation	29	Delayed	15.20	306.20
	Jaundice diminished; pain and fever gone; gallstone recovered from this 4 day collection	..	..	.....	..	.....	Trace	174.40
39	Removal of gallbladder and stones 4 years before; recurrent pain and jaundice 1 year before, short duration; present attack of jaundice and mild pain of 5 weeks' duration; no fever or leukocytosis; liver enlarged and firm	M	35	.....	48	Biphasic delayed	36.10	473.20
	After interval of 2 weeks	..	..	.....	20	.....	8.90	34.30
	Stone removed from common duct; liver finely granular	..	..	Operation				
40	Recurrent icterus; chills and fever; loss of weight; operation, no stone in common duct; autopsy: large stone impacted just above ampulla; biliary cirrhosis	F	63	Autopsy	22	Biphasic	7.50	9.00
41	Acute cholecystitis, febrile stage; leukocytosis; pain, tenderness and rigidity in right upper quadrant of abdomen	F	43	Operation	34	Biphasic prompt	112.30	10.50
	After interval of 5 days, with subsidence of acute symptoms and findings; multiple stones present in common duct at operation	..	..	.....	..	.....	2.10	

TABLE 1.—*Data on the Excretion of Urobilinogen—Continued*

Group 2. Obstructive Jaundice Due to Neoplastic Disease in Biliary Tract

Case	Condition	Sex	Age	Operation or Autopsy	Hemoglobin, %	Icterus Index	Van den Bergh Reaction	Urobilinogen Excretion, Mg. per Day	
								Urine	Feces
42	Repeated gallstone colic for past 11 years; multiple carcinomatous metastases (biopsy) in liver and adjacent to hepatic ducts; primary cause not determined; cholelithiasis	F	45	Operation	74	64	Biphasic prompt	Trace	1.60
43	Carcinoma of gallbladder with involvement of bile ducts and head of pancreas	M	72	Autopsy	74	150	Biphasic	0.04	0.13
44	Melanoma; metastases in common duct; none in liver parenchyma; large liver and finely granular surface	M	59	Autopsy	82	188	Biphasic prompt	1.60	17.90
45	Probable carcinoma of head of pancreas; definite evidence of hepatic metastases by thorium dioxide	M	68	.....	66	160	.....	Trace	0.70
46	Carcinomatosis of omentum, mesentery and retroperitoneal lymph nodes involving common bile duct; site of primary tumor not determined; no metastases in liver	M	75	Autopsy	91	192	Biphasic prompt	Trace	Trace
47	Carcinoma of head of pancreas	M	67	Operation	72	119	Biphasic prompt	0	4.70
48	Large retroperitoneal mass in region of head of pancreas, probably sarcoma (biopsy)	M	46	Operation	82	59	.....	Trace	1.90
49	Carcinoma, probably primary in pancreas; multiple hepatic metastases shown with thorium dioxide	M	49	.....	80	192	Biphasic	0	3.00
50	Carcinoma of head of pancreas	M	60	Autopsy	84	125	Biphasic prompt	Trace	0.57
51	Carcinoma of head of pancreas	M	63	Operation	77	127	Biphasic prompt	0	Trace
52	Previous gallstone colic; tumor filling common and hepatic ducts, microscopically adenocarcinoma; multiple stones in gallbladder	F	58	Operation	82	166	Biphasic	0	0.50
53	Painless jaundice of 6 months' duration; enlarged liver, ascites; operation revealed carcinoma involving ampulla of Vater and common hepatic bile ducts; biliary cirrhosis	F	46	Operation	76	122	Biphasic prompt	0	Trace
54	Jaundice; roentgen evidence of large gastric carcinoma; large nodular liver; blood in feces	M	59	.....	40	61	Biphasic	0.30	4.80
55	Carcinoma of head of pancreas (biopsy)	M	62	Operation	75	67	Biphasic prompt	0	Trace
56	Deep jaundice; carcinomatosis proved by biopsy of cervical lymph node; death; autopsy denied	M	54	.....	73	166	Biphasic	0	0
57	Jaundice for 3 months; carcinoma of gallbladder with metastases to liver	F	48	Autopsy	48	172	Biphasic prompt	0	1.50
58	Jaundice for 6 weeks; colic in right upper quadrant of abdomen; marked fever; operation: stones and purulent exudate in gallbladder; diffuse, hard infiltration of common duct; microscopically carcinoma	F	64	Operation	71	125	Biphasic	0	Trace
59	Jaundice for 2 weeks; epigastric pain; large, hard, nodular liver; widening of duodenal loop shown in roentgenogram; glycosuria; occult blood in feces; death; necropsy denied	F	64	.....	79	61	Biphasic	0	0.90

Group 3. Diffuse Hepatic Disease

A. Cirrhosis of Liver with Considerable Jaundice

60	Ascites; edema; hypertensive congestive heart failure; advanced cirrhosis of Laënnec type	F	56	Autopsy	62	40	Biphasic	18.70	75.00
61	Cinchophen cirrhosis; jaundice for 5 weeks; increasing ascites	F	53	.....	80	74	Biphasic delayed	8.10	211.50
	Six days later	..	..	.....	..	..	.....	8.08	

62	Cinchophen for arthritic pain during month before onset of jaundice; painless jaundice for 8 weeks; marked ascites; advanced atrophic cirrhosis	M	52	Autopsy	88	140	.....	3.80	29.70
	One week later	..	..	.....	..	..	.....	27.40	22.10
63	Jaundice for 6 weeks; splenomegaly; small liver (roentgenogram); melena; previous painless jaundice	F	12	.....	56	71	Biphasic delayed	1.70	8.10
64	Intermittent jaundice for 6 years; liver moderately enlarged, firm; spleen considerably enlarged	M	44	.....	82	60	Biphasic delayed	18.60	75.00
65	Attacks of jaundice since infancy; jaundice for 8 months; tonsillitis; sinusitis; fatal septicemia; no ascites; moderate anemia; advanced cirrhosis of Laënnec type	F	13	Autopsy	59	56	Biphasic delayed	Trace	14.10
66	Painless jaundice for 2 months; marked ascites	F	29	.....	90	77	Biphasic delayed	32.40	136.80
	Nine days later	..	..	.....	..	44	.....	1.10	102.00
67	Painless jaundice for 2 years; marked ascites for 9 months; small liver (thorium dioxide); palpable spleen	M	69	.....	63	50	Biphasic delayed	0.90	15.10
								4.40	
								1.50	
68	Mild intermittent jaundice for 3 or 4 years; ascites; splenomegaly; hemoglobin 58%; erythrocytes 2,830,000	M	48	.....	63	69	Biphasic delayed	49.00	124.40
69	Jaundice for 6 weeks; rapidly recurring ascites; coma and terminal hemorrhage from bowel; alcoholism; autopsy: advanced cirrhosis with numerous adenomas	F	46	Autopsy	72	136	Biphasic prompt	0.60	91.80

B. Various Types of Jaundice, with Clinical Signs Pointing to Cirrhosis and with Evidence of Increased Destruction of Blood

				Date					
70	Attack of painless jaundice 5 months previously; recurrence of 2 weeks' duration; enlarged spleen and liver; moderate ascites	M	52	10/15	87	40	Biphasic delayed	224.00	
				10/17	..	..	.....	80.20	
				10/19	..	..	.....	48.60	
				10/20	85	36	.....	10.30	777.00
				10/23	..	..	.....	52.30	
				10/25	..	..	.....	8.40	
				10/27	..	..	.....	.....	318.20
				10/29	..	..	.....	20.70	
				10/31	..	..	.....	30.30	
				11/ 1	..	..	.....	31.10	
				11/ 8	..	..	.....	38.90	
	Marked symptomatic improvement	..	..	11/13	..	..	.....	.....	307.00
				2/15	..	..	.....	50.40	136.90
				3/ 2	..	..	.....	24.60	
71	Painless deep jaundice for over 2 months; bilirubinuria; enlarged liver and spleen	F	31	10/16/34	85	179	Biphasic prompt		
				10/20	..	..	.....	.....	241.00
				10/21	..	..	.....	65.80	
				10/24	..	..	.....	.....	803.30
				10/28	..	..	.....	224.20	1,257.00
				11/ 1	..	104	.....	.....	461.20
				11/ 4					
				11/ 8	..	..	.....	211.00	990.00
	Definite macro-anisocytosis; reticulocytes 15%; erythrocytes 2,680,000	..	..	11/10	65	..	.....	.....	894.00
				11/12	..	43			
				11/16	..	35	.....	.....	146.20
				11/19					
				11/23	..	..	.....	23.60	

TABLE 1.—*Data on the Excretion of Urobilinogen—Continued*

Case	Condition	Sex	Age	Date	Hemoglobin, %	Icterus Index	Van den Bergh Reaction	Urobilinogen Excretion, Mg. per Day	
								Urine	Feces
71 (cont.)	Marked improvement; reticulocytes 2%	..	..	11/27/34	80	..	.....	35.50	
								3.80	
				1/12/35	77	14	.....	2.90	63.40
	Spleen and liver remain enlarged and firm	..	..	3/ 2/35					
	Spleen and liver smaller	..	..	4/23/35	83	11	.....	0.20	186.60
	Spleen and liver are still easily palpable; no jaundice; patient feels well	..	..	9/25/35					
72	Mild jaundice for 3 months; occasional vague distress in right upper quadrant of abdomen; abdominal distention; questionable ascites; small liver; enlarged spleen (thorium dioxide); erythrocytes 3,310,000	M	55	8/ 9/34	70	51	Biphasic prompt	251.40	56.20
				8/14	..	..	.....	56.20	
				8/15	..	..	.....	85.50	
				8/20	..	74			
				8/21	..	..	.....	72.70	
				1/18/35	..	..	.....	59.50	
				1/23	..	..	.....	.....	603.90
				4/13/35	..	23	.....	.....	470.00
73	Chronic alcoholism; jaundice; ascites; enlarged liver; spleen not palpable; erythrocytes 4,100,000	M	52	.....	84	91	Biphasic	108.10	319.70
74	Icterus for 2 weeks, never previously; marked hepatic and moderate splenic enlargement; bilirubin in urine at height of jaundice; reticulocytes 12%; repeated blood transfusions	F	63	9/ 7/33	32	80			
				9/ 9	..	..	.....	49.20	
				9/14	..	16	Indirect		
				9/26	38	..	.....	12.70	755.00
				9/29	..	20			
				12/ 2	68				
	Moderate ascites; no opportunity afforded for further urobilinogen studies	..	..	2/ 7/34	70				
75	Splenomegaly; marked enlargement of liver; slight ascites; anemia for 2 years; reticulocytes 7%	F	30	3/ 5	..	17	Indirect	29.50	500.20
	Erythrocytes 1,770,000	..	..	3/16	47	..	.....	.....	1,107.00
				4/12	..	..	.....	56.10	332.40
				5/14					
				5/16	..	..	.....	.....	952.00
				5/18	..	..	.....	19.20	
76	Chronic alcoholism; recurrent jaundice for 3 years; liver palpable; spleen markedly enlarged; mild edema of ankles; erythrocytes 2,900,000	M	45	....	62	56	.....	27.40	526.50
	C. Cirrhosis with Slight Jaundice								
77	Ascites for 1 month; enlarged liver and spleen	M	41	....	69	13	.....	7.00	
78	Enlarged spleen and liver; latter finely nodular	F	38	....	80	13	.....	10.20	
79	Mild jaundice for 16 months; first noticed when 7 months pregnant; advanced cirrhosis at autopsy	F	38	....	74	32	.....	17.00	55.00
80	Advanced hepar lobatum with marked ascites; autopsy: diffuse cirrhotic changes in small areas of liver between old gummas	M	48	....	..	20	Biphasic delayed	113.40	111.80

81	Enlargement of liver and spleen; moderate anemia; terminal Ludwig's angina; septicemia; marked diffuse cirrhosis at autopsy	F	46	....	59	24	Biphasic delayed	5.60	
82	Enlargement of liver and spleen; ascites; moderate anemia; leukopenia; low grade fever; right hydrothorax	F	41	....	64	14	.....	44.00	
83	Chronic alcoholism; ascites; leukocytes 3,350	M	52	....	62	11	.....	29.10	134.00
84	Chronic alcoholism; marked ascites; psychosis; accurate collection of urine and feces not certain	M	60	....	75	16	Biphasic	4.60	52.70
	D. Clinical Diagnosis of Acute Catarrhal Jaundice								
85	Painless jaundice for 2 weeks (possible cinchophen poisoning)	M	44	11/14	93	..	Biphasic prompt	3.80	10.20
	Jaundice clearing; feels much better	..	..	12/ 7	..	..	.....	206.80	280.00
86	Painless jaundice for 1 month	M	30	5/ 2	86	92	Biphasic delayed		
	Improving	..	..	5/ 9	..	32	.....	9.50	++
	Jaundice fading	..	..	5/18	..	16			
87	Painless jaundice for 2 weeks	F	21	10/21	80	130	Biphasic		
				10/24	..	100			
	Improving	..	..	11/ 2	..	65	.....	8.20	115.40
88	Painless jaundice for 10 days, now receding	M	22	.....	..	..	.....	8.00	
89	Painless jaundice for 1 week preceded by acute respiratory infection	M	27	11/22	99	107	Biphasic	11.20	20.50
				11/29	..	..	.....	28.80	
				12/ 6	..	45	.....	21.80	
	Improving; feels much better; jaundice almost entirely gone	..	..	12/17	..	..	.....	9.40	
90	Painless jaundice for 1 week; acholic stools; marked bilirubinuria	M	16	.....	..	..	.....	22.70	10.80
91	Painless jaundice following rheumatic fever; liver slightly enlarged; recovery	F	42	1/31	75	187	Biphasic	19.80	145.60
92	Jaundice for 4 days, preceded by nausea and vomiting; complete recovery in 2 weeks	M	21	.....	85	23	.....	15.90	
93	Mild jaundice; enlarged liver; mild psychosis	M	48	4/12	81	27	.....	128.10	268.90
	Feels well; no visible jaundice; liver not palpable	..	..	5/15	..	14	.....	0.50	188.00
94	Jaundice for 3 weeks	M	53	4/25	82	136	Biphasic		
	Mild epigastric distress	..	..	5/ 3	..	70	.....	29.10	15.00
	Improving	..	..	5/16	..	33			
95	Painless jaundice for 1 month; recovery	M	30	....	..	75	Biphasic	62.60	131.90
	Group 4. Congestive Heart Failure								
96	Hypertension, with coronary disease; ascites; large tender liver; slight icterus; marked orthopnea	F	58	.....	98	..	.....	56.10	
97	Probable hypertension; mild pulmonary congestion; moderate enlargement of liver; small amount of ascites	M	53	.....	98	26	Biphasic	11.10	
	Marked improvement with rest in bed and digitalis; liver smaller; ascites gone	..	..	.....	..	13	.....	0	
98	Rheumatic mitral and aortic valve defects; large, tender liver; ascites; edema; autopsy 2 months later: marked chronic passive congestion of liver	F	38	.....	76	0	.....	14.60	
99	Hypertension; anasarca; passive congestion of liver and spleen at autopsy	F	39	.....	..	29	.....	1.10	132.90
100	Rheumatic aortic stenosis and insufficiency, probable adhesive pericardium; improving at time of estimations	M	46	.....	75	12	.....	0	83.10
101	Hypertension; dyspnea; slight ascites; enlarged liver, not tender	F	48	.....	81	18	.....	0	

TABLE 1.—*Data on the Excretion of Urobilinogen—Continued*

Case	Condition	Sex	Age	Date	Hemoglobin, %	Icterus Index	Van den Bergh Reaction	Urobilinogen Excretion, Mg. per Day	
								Urine	Feces
	Group 4. Congestive Heart Failure—Continued								
102	Hypertension; large, tender liver; ascites; orthopnea; auricular fibrillation	F	55	.....	106	14	Delayed	35.60	
103	Mitral stenosis; enlarged, tender liver; moderate pulmonary congestion; icterus	F	38	.....	86	25	Delayed	9.40	211.20
104	Mitral stenosis; compensation restored after digitalization; liver still palpable, no longer tender	F	25	.....	90	24	Delayed	3.80	
105	Heart failure due to hypertension and coronary disease; liver enlarged, firm, moderately tender; slight icterus	M	63	.....	89	21	Delayed	38.00	259.00
	Two weeks later, much improved	..	..	.....	..	12	.....	1.30	
106	Hypertensive cardiac failure; massively enlarged and tender liver; jaundice; bilirubinuria	F	68	.....	94	25	.....	21.90	34.80
	Group 5. Miscellaneous Diseases of Liver								
107	Probably amyloid disease; very large, smooth liver; tuberculosis of spine and kidney; fever; albuminuria	M	40	.....	..	..	.....	19.00	
108	Banti's disease; death due to bleeding of esophageal varix; autopsy: diffuse fibrosis of very large spleen, liver apparently normal	M	24	.....	75	13	.....	13.20	
109	Toxic vomiting of pregnancy; jaundice; psychosis	F	42	8/ 8	75	39	.....	102.10	
				8/ 9	..	..	.....	133.10	
	Large amounts of dextrose (intravenous); insulin	..	..	8/10	..	20	.....	42.00	
				8/14	..	..	.....	62.00	
	Therapeutic abortion	..	..	8/23	..	11	.....	9.10	
				8/27	..	..	.....	4.60	
	Much improved	..	..	2/ 4	..	..	.....	0	
110	Syphilis; hepar lobatum; large liver; no jaundice; hematemesis; small amount of ascites	M	51	.....	..	..	.....	Trace	
111	Syphilis; probable hepatic gummas; no jaundice or ascites	F	41	.....	..	7	.....	1.40	
112	Syphilis; hepatic gummas with fever; no jaundice or ascites	F	30	.....	70	4	.....	2.70	
	Group 6. Carcinoma of Peritoneum or Liver With or Without Ascites and Without Jaundice								
113	Recurrent ascites; tumor cells in fluid; no jaundice	F	61	.....	80	..	.....	Trace	
114	Ascites; biopsy of nodule in abdominal wall showed metastatic carcinoma		52	.....	90	5	.....	Trace	
115	Autopsy: primary carcinoma of left lobe of liver of cholangioma type	F	49	.....	86	8	.....	0.15	
116	Multiple liver metastases from primary carcinoma of breast; large liver; metastases shown with thorium dioxide	F	54	.....	68	5	.....	1.90	
117	Primary carcinoma of stomach; enlarged, hard liver; no jaundice	M	74	.....	71	..	.....	0.70	
118	Carcinoma of stomach with multiple liver metastases at autopsy	M	63	.....	58	11	.....	0.48	

119	Ascites; chronic alcoholism; admitting diagnosis: hepatic cirrhosis; autopsy revealed large retroperitoneal sarcoma with peritoneal implants	M	68	.....	56	7	.....	0		
120	Anorexia for 3 months; loss of weight; marked ascites; long standing chronic alcoholism; autopsy: carcinoma of stomach, widespread metastases to liver and peritoneum	M	50	.....	81	4	.....	13.00		
121	Carcinoma of transverse colon; enormously enlarged liver due to diffuse carcinomatosis (autopsy)	F	24	.....	63	13	.....	27.60		
122	Ascites; autopsy: large carcinoma of stomach with diffuse metastases to peritoneum	F	63	.....	..	8	.....	3.40		
				Group 7. Hemolytic Jaundice						
				A. Familial or Congenital						
123	Splenomegaly; recurrent jaundice; microcytes; increased fragility	F	58	10/ 1	50	38	Delayed	3.30	318.00	
	Splenectomy	..	..	1/15	..	..	.....	2.10	793.80	
				1/18						
				2/15	77	..	.....	0.76	77.50	
124	Splenomegaly; chronic icterus; microcytes; increased fragility; reticulocytes 18%	F	8	4/15	53	26	.....	0.24	428.00	
	Splenectomy	..	..	5/ 3	..	21	.....	.....	1,001.00	
				5/18						
				5/28	..	..	.....	.....	15.70	
				7/18	88					
				12/14	..	..	.....	.....	130.00	
125	Father of patient no. 135; splenomegaly; jaundice; increased fragility of erythrocytes; 4 day collection of feces sent in for examination	M	40	5/22	..	..	.....	.....	1,424.90	
126	Jaundice since infancy; splenomegaly; microcytes; increased fragility; mother has large spleen and frequent jaundice	M	18	3/ 1/34	81	94	Indirect			
				3/12	..	93	Indirect	.....	705.00	
				3/19/35	90	43	.....	19.70		
127	Recurrent icterus and anemia for 3 years; splenomegaly; microcytes; increased fragility; one brother has increased fragility	M	22	11/21/33	54	20	Indirect			
				11/24	..	..	.....	1.00	1,140.00	
				11/30	45	32	.....	.....	1,220.00	
				12/12	78					
	Splenectomy	..	..	12/15/33						
	No icterus; patient in good health; feces sent in for examination	..	..	12/20/34	..	..	.....	.....	358.00	
128	Recurrent jaundice for 5 years; splenomegaly; increased fragility; microcytes; reticulocytes 15%; sister has disease	M	30	8/29/34	55	21	Indirect	2.30	570.40	
				9/ 3	..	..	.....	.....	1,009.40	
				9/ 5	..	32				
				9/ 8	..	..	.....	.....	620.80	
				11/ 9	32	..	.....	8.30	910.00	
				11/20	..	..	.....	.....	990.00	
				11/30	..	..	.....	.....	606.00	
129	Sister of patient no. 128; admitted because of ulcerative colitis with moderate diarrhea; 3 months pregnant; large spleen; microcytes; increased fragility	F	27	3/ 2	57	16	.....	.....	136.10	
130	Recurrent jaundice since infancy; splenomegaly; microcytes; increased fragility; father and one brother have evidences of disease	M	38	.....	56	18	Indirect	2.60	2,475.00	
131	Intermittent jaundice; splenomegaly; increased fragility; microcytes	F	15	7/ 8	27	17	Indirect	100.80	1,185.90	
	Splenectomy (weight 1,600 Gm.); cholelithiasis noted	..	..	7/24						
	Markedly improved	..	..	8/ 8	82	..	.....	0	616.00	
	Feels entirely well	..	..	10/10	..	..	.....	0	85.20	
132	Severe anemia; no jaundice; microcytes; increased fragility; reticulocytes 17%; splenomegaly	M	16	8/ 8	24	8	.....	Trace	792.90	
	Splenectomy	..	..	8/21						
	Markedly improved	..	..	9/10	74	..	.....	Trace	91.70	
				12/30	77	8	.....	.....	156.50	

TABLE 1.—*Data on the Excretion of Urobilinogen—Continued*

Case	Condition	Sex	Age	Date	Hemoglobin, %	Icterus Index	Van den Bergh Reaction	Urobilinogen Excretion, Mg. per Day	
								Urine	Feces
	Group 7. Hemolytic Jaundice—Continued								
	B. Acquired								
133	Hodgkin's disease for 2 years; severe anemia for 2 or 3 months; large, very tender spleen (recent infarct); macro-anisocytosis; frequent normoblasts; fragility normal; reticulocytes 38%; continuous fever	F	18	1/19	14				
				1/22	..	22	Delayed		
				1/23	35				
				1/25	..	..	.....	155.00	
	Repeated transfusions; temporary improvement.....	..	..	1/28	18	22	.....	44.00	507.00
	Spleen smaller, no longer tender; left pleural and pericardial effusions; anemia progressive; death; autopsy: small area of Hodgkin's disease in liver; marked lymph node involvement; multiple pale splenic infarcts related to obliterating endarteritis; marked congestion of splenic pulp; moderate diffuse hyperplasia and marked hemosiderosis of reticular and endothelial cells	..	..	2/ 5	..	..	.....	Trace	104.00
				2/ 8	..	13	.....	1.40	707.10
				2/14	..	..	.....	1.10	
				2/18	..	..	.....	.....	304.70
				2/19	25	..	.....	Trace	
				2/23	23				
134	Recurrent attacks of mild jaundice and abdominal pain for 5 years; no previous anemia; no jaundice in other members of family; spleen and liver not palpable; fragility normal on several occasions; average diameter of erythrocytes 8.86 microns; polychromatophilia; normoblasts; reticulocytes 15 to 29%; autohemagglutination; mass in left side of pelvis	F	18	2/28/35	32	42	Indirect	9.80	1,106.70
				3/ 2	36	..	.....	2.50	
				3/ 5	30	39			
				3/ 9	45	..	.....	.....	986.00
				Transfusions					
	Operation; removal of ovarian cyst containing 800 cc. of fluid rich in hematin; condition not improved by operation; anemia progressive; varying jaundice	..	..	3/11	59				
				3/12	39				
				3/17	34	27	Indirect	380.80	
				Transfusions					
				3/20	24	..	.....	34.50	
				Transfusions					
				3/26	34	..	.....	6.20	1,831.20
				Transfusions					
				3/29	23	69	Biphasic direct		
				4/ 4	28				
				4/ 5	31	..	.....	.....	1,180.80
				4/ 8	26	..	.....	26.20	461.10
				Transfusions					
	Splenectomy (weight 400 Gm.); microscopic examination: pulp congestion; hemosiderosis; liver normal in appearance	..	....	4/11	62				
				4/16	48	12	.....	138.00	
				4/18	46	..	.....	22.30	
				4/20	40	-6	Indirect	35.20	
				4/24	49	..	.....	0.90	
	Improving	..	..	4/25	53	..	.....	.....	1,540.00
				4/29	57	..	.....	0.60	
				4/30	56	..	.....	.....	536.20
				5/ 5	54	..	.....	.....	406.70
				5/10	60	19	.....	2.30	429.00
				5/22	66	19			
	Feels well; appetite and strength good; slight icterus persists; 3,600,000 erythrocytes	..	..	6/ 2	70				
				7/ 6/35	..	10	.....	.....	206.00
	Entirely well; no icterus.....	..	..	8/20/36	86	10			
135	Probable posttraumatic hematoma in left kidney; marked hematinemia; icterus? serum bilirubin 0.3 per 100 cc.; hematuria, also probable hematuria; recovery	M	19	.....	70	29	Indirect	0.60	1,010.00

RESULTS

Group 1. Cholecystitis and Cholelithiasis.—The determinations recorded for the subjects in groups 1 A and B demonstrate that the amount of urinary urobilinogen is only slightly increased in instances of jaundice due to stone, except when the jaundice has been severe and of at least several weeks' duration or when obstruction to the outflow of bile has been complicated by acute infection in the gallbladder or biliary tract. It is important to note that in no instance was complete biliary obstruction encountered in this group, although the stools were rather frequently acholic in appearance and in some instances were reported to show negative results of qualitative tests for urobilin and urobilinogen. This lack of complete obstruction is in striking contrast to its regular occurrence in jaundice due to cancer, as reflected in the estimations to be given presently. Case 28 in particular emphasizes the importance of recognizing this distinct difference. This patient was sent to the hospital with a diagnosis of carcinoma of the head of the pancreas, a diagnosis suggested by painless jaundice of six months' duration, accompanied with considerable emaciation. However, the presence of 10 mg. of urobilinogen per day in the feces even after a long period of continuous jaundice suggested the presence of a stone in the common duct, while the even larger amount in the urine was attributed to biliary cirrhosis. These diagnoses were verified at operation. A large and firmly impacted cholesterol stone was removed from the common duct. The liver was considerably enlarged and diffusely roughened. Six months later the liver was no longer palpable, and the patient appeared to be in good health. In case 36 an entirely similar condition was recognized preoperatively only because of the absence of complete obstruction in spite of long-enduring, deep jaundice. Again a large stone was removed from the common duct at operation. The same type of excretion of urobilinogen in case 40 led to the diagnosis of stone in the common duct, but at operation no stone could be found, the common duct simply being drained. In spite of this the patient died, and at necropsy a fairly large and tightly impacted stone was present in the common duct just above the ampulla.

Several of the determinations for the patients in group 1 as well as some for the following groups illustrate that the importance of the ratio of the urobilinogen in the feces to the urobilinogen in the urine must be clearly appreciated. This fact has been emphasized previously.[5] Perhaps the best example of its importance is case 26, in which biliary cirrhosis following stricture of the common duct was noted at autopsy. The urinary urobilinogen content was only moderately elevated (3.9 mg. per day), but when this is compared with the small amount in the feces (6.7 mg. per day), it is evident that the value for the urine is relatively high. The same is true in cases 28, 32 and 33.

The increased excretion of urobilinogen in the urine in instances of acute cholecystitis appears to support Graham's[6] conception of associated hepatitis. This is best illustrated in cases 25, 27, 30, 35, 37, 38 and 41. With subsidence of symptoms pointing to infection, the urobilinogen content rapidly decreases to normal levels, as noted in cases 30, 35, 37, 38 and 41. Cases 35, 37 and 38 illustrate characteristic changes in the excretion of urobilinogen which occur when a stone

5. Adler, A., and Bressel, M.: Urobilinogenbestimmung in Stuhl und Harnmittels der neuen Extraktionsmethode, Deutsches Arch. f. klin. Med. **155**:326, 1928. Watson.[1a]

6. Graham, E. A.: Hepatitis: A Constant Accompaniment of Cholecystitis, Surg., Gynec. & Obst. **26**:521, 1918.

is dislodged from the common duct or when a change in its position results in release of the biliary obstruction. The latter is best noted in case 37. Here a sudden diminution of the jaundice occurred, and with this there was a great increase in the amount of urobilinogen in the feces. There was an increased amount in the urine also, probably owing to the effect of residual cholangeitis on the parenchyma of the liver. It was believed that this patient had passed a stone; however, none was found in the feces, and at operation several days later a large stone was present in the greatly dilated common duct. At the time of operation the urinary urobilinogen content had decreased to an approximately normal value.

Group 2. Obstructive Jaundice Due to Neoplastic Disease of the Biliary Tract.—In sharp contrast with the foregoing findings are those obtained for patients with jaundice due to neoplastic biliary obstruction, as shown in group 2. With only one exception the values in group 2 are uniformly low for both urine and feces. By comparison with the findings already given for jaundice due to stone and with those to be given later for jaundice due to hepatic disease, it is readily seen that an obstruction to the outflow of bile of this degree is probably rarely encountered in other conditions. It was realized that jaundice due to neoplasm is regularly more marked and more continuous (von Müller [7]), but the reliability of this evidence of complete obstruction for the diagnosis of neoplasm was not fully appreciated at the outset of this investigation. Thus, a diagnosis of stone in the common duct was made in case 42, chiefly because of the history of repeated previous attacks of gallstone colic. At operation carcinomatosis of the liver, with involvement of the hepatic ducts, as well as cholelithiasis, was present. Apart from the fact that this patient had been jaundiced for a considerable period, nothing suggested the diagnosis of neoplasm except the evidence of complete obstruction yielded by the estimations of urobilinogen. Later, similar instances (cases 52 and 58) were observed in which prior to the determinations of the urobilinogen, a diagnosis of stone in the common duct had been made. Because the results indicated complete obstruction, the presence of neoplasm was believed likely. At operation the gallbladder was found to contain stones, apparently supporting the first diagnosis; the common and hepatic ducts, however, were filled with tumor, microscopically adenocarcinomatous. Another illustrative case has been observed since group 2 was compiled and may be described briefly as follows. A man aged 60 had pain in the right upper quadrant of the abdomen of several weeks' duration four months before he was admitted to the hospital. The pain was intermittent and somewhat colicky. There was increasing jaundice for two months. The icterus index was 163. The urobilinogen excreted in the feces was 1.7 mg. per day, and none was excreted in the urine. A diagnosis of neoplastic obstruction was made, and laparotomy was performed for the purpose of making a palliative anastomosis. At operation it was believed that a small neoplasm could be palpated in the upper portion of the common duct. The patient died several days later; at necropsy there appeared to be only a benign stricture of the cystic and hepatic ducts at their junction. The gross appearance was not suggestive of neoplasm. However, a small scirrhous carcinoma was revealed on microscopic examination.

Because of ascites with enlargement of the liver, the initial clinical diagnosis in case 53 was cirrhosis of the liver. The results of the determinations of urobilinogen, however, strongly suggested a carcinomatous biliary obstruction. This was corroborated at operation.

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7. von Müller, F.: Ueber Ikterus, Jahresb. d. schles. Gesellsch. f. vaterl. Cult. (Med. Sect.) **70**:1, 1893.

In only one of the cases in group 2, i. e., case 44, was more than 5 mg. of urobilinogen found daily in the feces. In most cases the values were much lower than this, and the amount in the urine was practically negligible. In case 44 the incomplete obstruction was readily explained at necropsy by the fact that melanomatous metastases in the common bile duct, from a primary melanoma of the ear, were soft and somewhat polypoid, permitting bile to pass into the duodenum.

In the next group of cases, i.e., those of jaundice due to primary hepatic disease, the findings were again in definite contrast with those already noted in the various instances of extrahepatic obstructive jaundice. As compared with jaundice due to neoplasm, the obstruction to the outflow of bile was in no instance complete, while the amount of urobilinogen in the urine was regularly higher than for the cases of uncomplicated jaundice due to stone.

Group 3. Diffuse Hepatic Disease.—The cases in group 3 were divided into four parts, as indicated in table 1. With only an occasional exception, the urinary urobilinogen content in the cases in group 3 was relatively or actually markedly increased. The lack of increase in cases 65 and 69 could not be accounted for; however, necropsy in each instance revealed a cirrhotic liver which was remarkably adenomatous, and it is possible that these ademonas were functioning so far as the removal of urobilinogen was concerned, while the jaundice could be related to mechanical obstruction due to fibrosis. Since the accompanying table was compiled, two cases of severe acute catarrhal jaundice have been studied in which the amount of urobilinogen in the urine was less than 1 mg. In one of these the amount in the feces was 15 mg. per day; in the other, 9 mg. It is probable that the amount of urobilinogen reabsorbed from the bowel in these instances was excessively small or at least sufficiently small so that the liver, although damaged, was capable of its disposal. In both instances the amount of urobilinogen in the feces was sufficiently large to aid materially in excluding neoplasm as the cause of the jaundice.

In only one case of parenchymal jaundice (an instance observed since the accompanying table was compiled) was the amount of urobilinogen in the feces in the low range characteristic of neoplastic obstruction. This patient, a man aged 61 years, had been given five injections of neoarsphenamine (0.15 Gm. each) in the hope of improving a urinary infection. Shortly after the last of these injections he became jaundiced. The estimations of urobilinogen yielded the following data:

Date	Icterus Index	Urobiliongen, Mg. per Day	
		Feces	Urine
1/22	67	3.1	0.5
1/27	88		
2/3	101		
2/6	88	4.7	41.5
2/12	64	57.0	54.2
2/28	25	77.9	6.4
3/10	21		7.1
3/12			5.1

This case illustrates the importance of (1) evaluating even small amounts of urinary urobilinogen in the presence of high grade biliary obstruction and of (2) repeated estimation of the urobilinogen content, particularly in the feces, in doubtful cases.

In other instances of marked jaundice, such as cases 85, 89 and 90, the importance of noting the stool-urine ratio must be reemphasized.

Fluctuation in the amount of urinary urobilinogen from day to day, noted previously by Wilbur and Addis,[8] was observed rather frequently in the foregoing instances in which more than one determination was made. Cases 62, 67, 70, 71 and 72 are illustrative.

In cases 70 and 72 the urinary urobilinogen content decreased markedly after a short period of rest in bed, without any appreciable change in the degree of jaundice. In several cases the urobilinogen content decreased to a normal value coincident with marked clinical improvement. In one of these (case 66) the presence of ascites with jaundice led to a diagnosis of cirrhosis, the use of salyrgan resulted in prompt disappearance of the ascites, and although mild jaundice persisted, the urobilinogen value rapidly decreased to normal. In another (case 71) the urobilinogen value became normal, although the liver and spleen remained considerably enlarged. These facts are mentioned since they illustrate that the urinary urobilinogen value is not always elevated in the presence of other signs of hepatic disease. At the same time, it is believed that a marked decrease, such as has been described, points to an increase in the function of the liver.

The results recorded in group 3 B are of particular interest, since they illustrate the increased rate of destruction of blood which may accompany cirrhosis of the liver. At first glance it might seem possible that the considerable increase in the urobilinogen content of the feces in these cases could be explained by at least temporary release of a biliary obstruction. Friedrich von Müller[7] first demonstrated the increased output of urobilin following release of an obstruction due to stone or in catarrhal jaundice. Such instances are represented in the present investigation, viz., cases 35, 37, 38 and 85.

It is believed, however, that the high values noted in group 3 B were related not to fluctuations in the flow of bile but rather to an actual increase in the rate of destruction of the blood. The reason for this belief may be stated as follows: The amounts excreted in the feces were often much larger than has been noted in cases in which the release of a biliary obstruction was known to have just occurred. In fact, the values are frequently as great or greater than those to be given later for hemolytic jaundice. In some instances the increased excretion of urobilinogen occurred at a time when there was no evidence of a decrease in the degree of biliary obstruction. In case 71, in which there was exhibited the greatest increase of urobilinogen in the feces in this group, definite macrocytic anemia of a regenerative type developed during the period of increased excretion. This later disappeared as the excretion of urobilinogen markedly decreased.

The values noted in cases 70, 71 and 72 suggest that the increased destruction of blood proceeds at a variable rate.

Group 4. Congestive Heart Failure.—The limited data obtained in this investigation concerning the excretion of urobilinogen in congestive heart failure demonstrate only that urobilinuria is not of constant occurrence. In the eleven patients studied it appeared that tenderness of the liver was the only finding regularly noted with an increase of urobilinogen in the urine. Weiss[9] pointed out that urobilinuria is usually more marked when there is decompensation due to a defect in the mitral valve than when it is due to aortic incompetence. Weiss observed also that urobilinuria in heart failure is at times slight, and he said he believed that this is due either to a lack of passive congestion of the liver or to accompany-

8. Wilbur, R. L., and Addis, T.: Urobilin: Its Clinical Significance, Arch. Int. Med. **13**:235 (Feb.) 1914.

9. Weiss, M.: Ueber Urobilin und seine diagnostische Verwertung, Wien. Arch. f. inn. Med. **20**:39, 1930.

ing renal insufficiency. In the foregoing instances in which the urobilinogen value was not increased in the urine (cases 99, 100 and 101) neither of these conditions appeared to have been fulfilled, and the low values in these cases cannot be explained. In five instances the amount of urobilinogen in the feces was not elevated, so that in these there was no reason to consider the jaundice due to an increased destruction of blood. The latter possibility was suggested by Eppinger,[10] who found an increased amount in the feces in several cases of heart failure. Weiss [9] also mentioned a "tendency" to an increased excretion of urobilin in the feces in heart failure. With the exception of the five determinations mentioned, which do not indicate an increased rate of blood destruction, the present investigation does not include data relative to this question. The omission of estimations for the stools in the other instances is due to the difficulty in obtaining accurate collections.

Group 5. Miscellaneous Hepatic Diseases.—Group 5 includes various types of hepatic disease which could not be classified with the foregoing instances. In the case of Banti's disease it was of interest that the liver at autopsy did not exhibit any recognizable pathologic change. In spite of this, considerable urobilinogen was present in the urine, whether owing to a functional disturbance secondary to splenic disease or to anoxemia because of hemorrhage cannot be determined. This observation simply indicates that urobilinuria with Banti's disease is not necessarily on the basis of hepatic cirrhosis.

In none of the three cases of hepar lobatum in group 5 was the urobilinogen value increased for the urine. In all of these cases the liver was enlarged and jaundice was absent. When contrasted with case 80 in group 3 C, in which the liver was extremely small and almost completely replaced by scar tissue, the urine containing a large amount of urobilinogen, it is evident that an increase in the urobilinogen content may be expected only in an advanced stage of the disease or when the replacement of liver by gummas is widespread.

Group 6. Carcinoma of the Liver or Peritoneum.—The determinations in the cases in group 6 indicate that the estimation of urinary urobilinogen is of considerable value in the differentiation of ascites due to diffuse hepatic disease from that due to peritoneal carcinomatosis. The determinations indicate that ordinary carcinomatosis of the liver rarely interferes with its function of urobilinogen excretion. In one instance of diffuse hepatic carcinomatosis a fairly large amount of urobilinogen was present in the urine (case 121). Case 120, in which carcinomatous metastases were present in the liver and on the peritoneum, illustrates that the urinary urobilinogen value may occasionally be elevated to the range characteristic of diffuse hepatic disease such as cirrhosis. In this instance necrosis was prominent in the widespread areas of tumor and may have been responsible for the hepatic damage and urobilinuria.

Group 7. Hemolytic Jaundice.—Thirteen cases of hemolytic jaundice were studied in addition to the cases already mentioned in which an increased destruction of blood accompanied cirrhosis of the liver. In ten of these cases the criteria for the diagnosis of familial hemolytic jaundice were fulfilled, while in the other three the condition was of the acquired, or secondary, type. The former are included in group 7 *A* and the latter in group 7 *B*. In all but one of the instances in group 7 the excretion of urobilinogen in the feces was markedly increased. The exception, case 129, was the case of a patient who was suffering principally from ulcerative colitis and in whom the hemolytic activity appeared to be quiescent.

10. Eppinger, H.: Die hepatolienalen Erkrankungen, Berlin, Julius Springer. 1920.

Of particular interest in the group of subjects with hemolytic jaundice was the relatively small amount of urobilinogen in the urine in the majority of cases. In the instances in which considerable increases occurred, factors other than a simple increase in the rate of destruction of blood appeared to be significant. The question of urobilinuria as a result of "overflow" alone will be discussed in more detail in the following pages.

COMMENT

In a recent consideration of painless jaundice Ottenberg[11] stated that there is at present "no clinical or laboratory method of distinguishing partial or complete obstruction of the bile duct from partial or complete suppression of bile." By this he undoubtedly referred to the difficulty often encountered in distinguishing jaundice due to hepatic damage from that due to simple obstruction in the biliary tract. The

TABLE 2.—*Usual Range of Urobilinogen Excretion in the Common Forms of Jaundice*

	Urobilinogen, Mg. per Day	
	Urine	Feces
1. Jaundice due to obstruction in biliary tract		
Stone, without complications	0-6	10-250
Stone, with complications such as cholangeitis, biliary cirrhosis and anemia	4-50	10-250
Neoplasm	0-0.3	0-5
2. Jaundice due to diffuse hepatic disease		
Cirrhosis	4-100	8-200
Cirrhosis or hepatic disease with increased blood destruction	20-200	300-1,200
Acute catarrhal jaundice	4-200	10-300
3. Hemolytic jaundice		
Uncomplicated	1-10	300-1,800
Complicated by infectious disease, severe anemia, infarction or anesthesia and during "hemolytic crises"	10-300	300-2,500

results of the present investigation indicate that a determination of the per diem excretion of urobilinogen in the urine and feces, in conjunction with other clinical data, usually makes possible the distinction of these common forms of jaundice. In general, they are characterized by urobilinogen values of the magnitude shown in table 2.

In previous investigations of obstructive and hepatic jaundice with reference to the excretion of urobilinogen, attention was given chiefly to the amounts present in the urine, and little information has accumulated concerning the variations in the urobilinogen content of the feces in these forms of jaundice. Since the early studies of Friedrich von Müller,[7] it has been generally recognized that tests for urobilin and urobilinogen in both feces and urine are most apt to be negative when jaundice is due to neoplasm. However, there has been little recognition of the characteristic quantitative differences in the excretion of urobilinogen existing between jaundice due to neoplasm, on the one hand, and jaundice due to stone or diffuse hepatic disease, on the other.

11. Ottenberg, R.: Painless Jaundice, J. A. M. A. **104**:1681 (May 11) 1935.

The results of the present investigation indicate that the amount of fecal urobilinogen with the former is almost never more than 5 mg. per day and that not more than a trace of urobilinogen is found in the urine, while the value for fecal urobilinogen in the latter forms was rarely less than 10 mg. and in but one instance below 5 mg. In these types the amount in the urine varies with the degree of hepatic dysfunction but may be small even in the presence of a damaged liver if the amounts of bile permitted to enter the intestine are greatly reduced. Absence of urobilinogen from the urine, although a regular finding in cases of jaundice due to neoplasm, cannot be considered peculiar to this group, since it is noted also at times with varying degrees of obstructive jaundice due to stone (cases 7, 12, 13, 14 and 15) and rarely with high grade obstructive jaundice due to cirrhosis (cases 65 and 69).

In considering the findings of complete biliary obstruction, which appear to be so characteristic of jaundice caused by a neoplasm, the question at once arises as to how long the jaundice must be present before these criteria obtain. As yet this question cannot be answered, exactly, since in no instance in this study has jaundice due to neoplasm developed under observation. In several instances, however, it was of not more than two weeks' duration, and in each of these complete biliary obstruction was already present (less than 5 mg. of urobilinogen per day was excreted in the feces). It is probable that the interval between the appearance of jaundice and the development of complete obstruction is short, since the onset of jaundice points to an already considerable narrowing of the common bile duct or hepatic ducts. With the progressive constriction or plugging or both which a neoplasm regularly causes, the biliary outflow is soon totally obstructed, and the traces of urobilinogen which are found in the feces thereafter are best explained as originating from bilirubin in bile-stained epithelial cells of the intestinal tract (Gerhardt,[12] Wallace and Diamond[13] and McMaster and Elman[14]). The different mechanism obtaining in jaundice due to a stone, i.e., obstruction without constriction, the ensuing dilatation of the duct permitting at least occasional egress of small amounts of bile even when the stone is impacted (as in cases 28 and 40), is reflected in the excretion of urobilinogen in the feces, which in this series was never less than 9 mg.

Patients with jaundice due to neoplasm not infrequently state that the jaundice has become less intense or that it varies in intensity. This, together with a measurable reduction in the serum bilirubin, has often

12. Gerhardt, D.: Ueber Urobilin, Ztschr. f. klin. Med. **32**:303, 1897.

13. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:689 (June) 1925.

14. McMaster, P. D., and Elman, R.: Studies on Urobilin Physiology and Pathology: II. The Derivation of Urobilin, J. Exper. Med. **41**:513, 1925.

led to the inference that there has been a partial release of the biliary obstruction. It is conceivable that this could be effected by necrosis in a tumor or a decrease in size because of some other factor.[15] On the other hand, unless this release were proved by the reappearance of more than traces of urobilinogen in the feces, the fluctuations of bilirubin in the blood are more readily explained by variations in the rate of the destruction of blood. Rous and Drury [16] produced complete biliary obstruction in dogs and then demonstrated that the amount of jaundice was proportional to the wastage of erythrocytes. Induced hemorrhage resulted in a diminution of the jaundice, and the administration of hemolytic agents resulted in a prompt increase of the jaundice. In our cases of obstructive jaundice due to neoplasm (group 2) it will be noted that wide variations in the degree of icterus were present, although the biliary obstruction was complete in all cases but one. The icterus indexes in this group ranged from 59 to 192. One patient (case 55) stated that the jaundice had diminished markedly in the month prior to his admission to the hospital, and in support of this statement the icterus index was found to be only 67. However, the biliary obstruction was complete, since urobilinogen was lacking in the urine and feces. In addition to the direct evidence of Rous and Drury,[16] indicating that there is diminished jaundice following hemorrhage (case 54 probably illustrates this), there is also reason to believe that a compensatory decrease in the rate of the destruction of blood occurs in conditions associated with cachexia, low grade infection or inactivity, even in the absence of anemia. This was indicated in paper II of this series.[1c] In the cases of neoplastic biliary obstruction, in which the icterus index was relatively high even in the presence of anemia, such as is illustrated in case 45, two possibilities must be considered; (1) an added hemolytic factor and (2) a slower urinary excretion of bilirubin. No information has been obtained in this study to indicate the possible importance of either of these.

15. One instance of this type has been observed recently. A woman aged 64 years was first seen in January 1935, when she complained of painless jaundice of three weeks' duration. The amount of urobilinogen excreted in the feces was 0.5 mg. per day, and none was present in the urine. At operation carcinoma of the common duct was present. The patient survived the operation, but with persistent deep jaundice and later ascites (for fourteen months). The urobilinogen in the feces on Jan. 15, 1936, amounted to 4.8 mg. per day, with only a faint trace in the urine. Later, pain and tenderness developed in the right upper quadrant of the abdomen, with some rebound tenderness. On February 26 the urobilinogen content of the feces was 77.6 mg. per day, 4.2 mg. per day being present in the urine. These findings indicated partial relief of the biliary obstruction, but whether it was due to necrosis or to biliary fistula into the bowel remained undetermined, as permission for necropsy could not be obtained (death occurred on March 13).

16. Rous, P., and Drury, D. R.: Jaundice as an Expression of the Physiological Wastage of Corpuscles, J. Exper. Med. **41**:601, 1925.

McMaster and Elman [17] demonstrated that infection of the biliary tract in dogs was at times responsible for the local formation of urobilin. From this it was conceivable that urobilin might be present in the urine in spite of complete biliary obstruction. However, no instance has been found in the present investigation in which only the urine and not the feces contained urobilinogen. In certain instances determinations were not made on the feces, but in these the degree of jaundice was not sufficient to suggest the presence of complete biliary obstruction. The possibility is not excluded that a portion of the urinary urobilinogen was formed in the biliary tract in cases in which biliary infection was present. In one instance (case 41) this was strongly suggested by the great disparity between the urobilinogen content of the urine and that of the stool, the former being 112 mg. when the latter was but 10.5 mg.

The occurrence of a marked increase in the urobilinogen content of the feces in certain cases of hepatic disease deserves particular mention. Bleichröder [18] first noted that the bone marrow is usually red in cases of hepatic cirrhosis, and Gauckler [19] later described histologic changes in spleens from patients with cirrhosis, which he attributed to an increased destruction of erythrocytes. He emphasized also the hemosiderosis of both spleen and liver which may occur in cases of cirrhosis. This subject was reviewed by Eppinger,[10] who offered considerable evidence in support of Gauckler's views and who clearly demonstrated that an increased excretion of bilirubin into the bile and of urobilinogen in the feces occurs in some cases of cirrhosis. Eppinger [10] apparently believed that this increased destruction of blood was limited to those cases of cirrhosis as described by Hanot, i. e., hypertrophic cirrhosis with jaundice and splenomegaly, but without ascites. He also stated that the jaundice in patients with such a condition is often in large part hemolytic and pointed to spectacular improvement with the disappearance of jaundice following splenectomy. Of the patients with hepatic disease in group 3 B who showed an increased amount of urobilinogen in the feces, some exhibited enlargement of the liver, while in others the liver was smaller than normal. However, in each of the instances in which definite hemolytic anemia was present the liver and spleen were considerably enlarged and jaundice was present, but there was no ascites. To this extent the present findings correspond with those of Eppinger. In two cases of atrophic cirrhosis, however, the excretion

17. McMaster, P. D., and Elman, R.: Studies on Urobilin Physiology and Pathology: VI. The Relation of Biliary Infections to the Genesis and Excretion of Urobilin, J. Exper. Med. **43**:753, 1926.

18. Bleichröder, R.: Ueber Lebercirrhose und Blutkrankheiten, Virchows Arch. f. path. Anat. **177**:435, 1904.

19. Gauckler, E.: Les modalités histologiques de l'hématolyse et le rôle de la rate dans l'évolution du pigment sanguin, Arch. d. mal. du coeur **1**:401, 1908.

of urobilinogen in the feces was definitely increased; ascites was present in one of these. Consequently, it does not appear that an increased destruction of blood can be regarded as a means of distinguishing a particular variety of cirrhosis. More attention should be given to determining whether the patients with cirrhosis showing an increased destruction of blood are those who are most benefited by splenectomy.

In the recent literature much interest has centered on the macrocytic anemia which may occur with cirrhosis of the liver. Eppinger [10] in 1920 pointed out that a pernicious type of anemia is at times seen with cirrhosis of the liver. A striking example of this was a case reported in 1928 by Walterhöfer, Plenge and Neuberger.[20] Wintrobe and Shumacker [21] and Van Duyn [22] have recently observed similar instances and have collected reports of others from the literature. So far as can be determined only one case of macrocytic anemia with cirrhosis of the liver has been studied with reference to the excretion of urobilinogen. This case, recently reported by van den Bergh and Kamerling,[23] has many points in common with case 71 in the present series. In both cases macrocytic anemia developed in the course of an illness characterized by jaundice, enlargement of the liver and of the spleen and a greatly increased excretion of urobilinogen in the feces and urine. While van den Bergh and Kamerling's case terminated fatally, in the case reported here the improvement was remarkable, although the liver and spleen remained enlarged and firm. The increased destruction of blood in this instance did not persist, and it will be noted that this overactivity appears to be in some degree cyclic in other cases of this type as well (cases 70 and 72). In six of the seven cases of hepatic disease with increased urobilinogen in the feces, some information as to the size and hemoglobin content of the erythrocytes was obtained. The color index was more than 1 in five of these (cases 71, 72, 73, 75 and 76), while in one instance (case 74) it was 0.8. Measurements of the average diameter of the erythrocytes were carried out in four cases with the aid of a Whipple eyepiece micrometer. The results were as follows: 8.25 microns in case 71. (Unfortunately this measurement was not made until the patient had greatly improved. Obvious macrocytosis with a

20. Walterhöfer, C.; Plenge, K., and Neuberger, J.: Ueber einen Fall von Biermersche Anämie mit schwerer Lebererkrankung, Deutsches Arch. f. klin. Med. **159**:306, 1928.

21. Wintrobe, M. M., and Shumacker, H. S.: The Occurrence of Macrocytic Anemia in Association with Disorder of the Liver, Bull. Johns Hopkins Hosp. **52**:387, 1933.

22. Van Duyn, J., Jr.: Macrocytic Anemia in Disease of the Liver, Arch. Int. Med. **52**:839 (Dec.) 1933.

23. van den Bergh, A. A. H., and Kamerling, A. W. C. S.: Lebercirrhose met haemolytische anaemie en massale haematinaemie, Nederl. tijdschr. v. geneesk. **78**:4434, 1934.

high color index was noted at the height of the illness.), 8.77 microns in case 72, 8.35 microns in case 75 and 8.31 microns in case 76. A number of control measurements for normal subjects yielded values varying between 7.4 and 7.9 microns. Consequently it appears that the majority of these patients who showed an increased destruction of blood with hepatic disease exhibited macrocytosis in varying degree.

The frequent presence of an increased amount of urobilinogen in the urine in hemolytic jaundice has long been recognized. The conception that this increase is due to simple "overflow" or overloading of the liver with urobilinogen is said by Eppinger [10] to have originated in the Italian school, Riva and Zoja in particular championing the view that urobilinuria parallels the destruction of blood. Brugsch and Retzlaff [24] and later Eppinger [10] emphasized that dysfunction of the liver probably plays an important rôle in the association of urobilinuria with increased destruction of blood. The experimental work of Elman and McMaster [25] appeared to support the earlier view, but it is doubtful whether dysfunction of the liver could be as well excluded in their experiments as it is in many instances of human hemolytic jaundice. In this regard, Mann and Bollman [26] have recently expressed doubt that hemolytic jaundice as seen clinically can be reproduced experimentally. Furthermore, the earlier work offered in support of the conception of simple "overflow" did not take into account the important effects of anoxemia on the liver, such as have been adequately demonstrated by Rich and his co-workers.[27] Rich gave as his belief that the urobilinuria in hemolytic jaundice is due in part to excess (overflow) and in part to the subnormal function of the liver. The results of the present investigation indicate that the latter factor is the more important one. A marked increase in the rate of destruction of blood alone, as evidenced by an increase in the urobilinogen content of the feces, cannot be considered the cause of an appreciable increase in the amount of urobilinogen in the urine, since many instances were observed in which a large amount was present in the feces, together with other evidence of an increased destruction of blood but in which the amount of urobilinogen in the urine was small. Only four of the patients with hemolytic jaundice in group 7 exhibited a considerable amount of

24. Brugsch, T., and Retzlaff, K.: Blutzerfall, Galle und Urobilin: Zur Frage der Gallenfarbstoffbildung aus Blut, Ztschr. f. exper. Path. **11**:508, 1912.

25. Elman, R., and McMaster, P. D.: Studies on Urobilin Physiology and Pathology: V. Relations Between Urobilin and Conditions Involving Increased Red Blood Cell Destruction, J. Exper. Med. **42**:619, 1925.

26. Mann, F. C., and Bollman, J. L.: Jaundice: A Review of Some Experimental Investigations, J. A. M. A. **104**:371 (Feb. 2) 1935.

27. Rich, A. R.: The Pathogenesis of the Forms of Jaundice, Bull. Johns Hopkins Hosp. **47**:338, 1930.

urobilinuria. In three of these the increases occurred during periods when factors other than a simple increase in the destruction of blood were prominent. Thus, in case 133 a large amount of urobilinogen was present in the urine at the same time that symptoms and signs referable to recent splenic infarction were dominant in the clinical picture. As these subsided the urobilinogen content of the urine decreased rapidly to a normal amount, although the hemolytic anemia persisted. Such an instance suggests that substances from infarcts in other organs may temporarily interfere with the function of the liver. A similar view was advanced by Schiller [28] to explain a marked increase in the urobilinogen content of the urine in a case of large hematoma due to ectopic pregnancy. A case of repeated pulmonary infarction following the development of coronary thrombosis and a mural thrombus has recently been studied with reference to the excretion of urobilinogen.[29] The attending physician noted a marked increase in the amount of urobilinogen in the urine shortly after the onset of signs and symptoms of infarct. This disappeared as the patient's condition improved. Subsequently another infarct occurred and at this time the amount of urobilinogen in the urine was estimated repeatedly (the data in this case are not included in the foregoing tables).

Date	
3/24	Onset of signs of pulmonary infarct (pain in chest, hemoptysis, râles and friction)
3/26	Mild jaundice
3/27	Urinary urobilinogen, 75.9 mg. per day
3/28	Urinary urobilinogen, 39.6 mg. per day
3/29	Urinary urobilinogen, 27.5 mg. per day
3/30	Patient improving
4/ 4	Urinary urobilinogen, 0.7 mg. per day
4/1 to 4/ 4	Urobilinogen in feces, 224.2 mg. per day

It is evident, however, that extravasation of blood which results in jaundice or an increased excretion of urobilinogen in the feces is not always accompanied with increased amounts of urobilinogen in the urine. This is illustrated by case 135, in which trauma adjacent to the left kidney resulted in hematuria with hematinemia. It is of interest that no increase in the excretion of bilirubin could be demonstrated in the serum, and the elevated icterus index and the patient's color were obviously due to the hematin present (readily identified by the hemochromogen spectrum). This has been spoken of as "hematin icterus," and were it not for the marked increase of the urobilinogen content of

28. Schiller, W.: Zur Entstehung der Urobilinogenurie, Wien. Arch. f. inn. Med. **12**:417, 1926.

29. Dr. D. P. Head, of Minneapolis, gave me the opportunity of carrying out the determinations in this instance.

the feces, it would lend support to the belief of Duesberg [30] that hematin is not formed in the transition of hemoglobin to bilirubin. In spite of the excessive formation of urobilinogen, the amount in the urine remained normal.

In case 134 a marked temporary increase in the excretion of urobilinogen occurred after each of two laparotomies carried out with the patient under general anesthesia. There was no bowel movement for a number of days after the operation, so that both an increased resorption of urobilinogen and a disturbed hepatic function incident to the combined anoxemic effect of anemia and anesthesia must be recognized as important in explaining the large amounts of urobilinogen which appeared in the urine for short periods. There is little doubt that reabsorption of urobilinogen from the bowel is in considerable measure dependent on the rate at which the feces move through the lower portion of the intestinal tract. In the presence of injury to the liver the associated urobilinuria is much more marked if constipation, intestinal obstruction or ileus exist. The following case is illustrative: A woman aged 48 had postpneumonic empyema and possibly an abscess in the lower lobe of the left lung. Chills and fever, marked anemia, ileus with distention and infrequent small bowel movements were noted. The urinary urobilinogen content was 312 mg. per day, and the urobilinogen content of the feces was 9 mg. per day. The latter value was doubtless low, in part because of the relatively small amount of feces collected; nevertheless, it is evident that the great majority of urobilinogen was reabsorbed from the bowel and refused by the liver.

Only one of the patients with hemolytic jaundice (case 126) exhibited considerable urobilinuria in the absence of obvious factors believed to decrease the function of the liver. It is important to note, however, that this patient had continuous marked jaundice, the icterus index varying between 43 and 94. The van den Bergh reaction was indirect, and bilirubin was not found in the urine. The marked hyperbilirubinemia, without anemia, strongly suggested that the function of the liver was disturbed, at least so far as the rate of bilirubin excretion was concerned. In striking contrast are the findings in case 132; here the reverse is noted, i. e., marked anemia without jaundice. The absence of any increase of bilirubin in the blood in spite of the greatly increased destruction of blood can be regarded as due only to an increased ability of the liver to clear the circulating blood of bilirubin and thus prevent the appearance of jaundice. In accord with this conception is the fact that the urobilinogen value did not increase for the urine in this instance, although it was greatly increased for the feces (prior to splenectomy).

30. Duesberg, R.: Ueber die biologischen Beziehungen des Hämoglobins zu Bilirubin und Hämatin bei normalen und pathologischen Zuständen des Menschen, Arch. f. exper. Path. u. Pharmakol. **174**:305, 1934.

In the cases of familial hemolytic jaundice in which splenectomy was performed the effect on the excretion of urobilinogen in the feces is clearly illustrated. Eppinger[10] first demonstrated the marked decrease which occurs. This was also observed in one case by Goldschmidt, Pepper and Pearce.[31] These investigators studied the excretion of urobilinogen shortly after splenectomy. The present results are of interest because they also afford some idea of the rate of destruction of blood many months after splenectomy. It appears that splenectomy in the familial type of hemolytic jaundice usually effects a prompt reduction of the urobilinogen in the feces. In certain instances (case 124) the reduction is extreme, making it appear that the spleen had been practically the only site of blood destruction; in one instance, however, the amount was still considerably elevated two weeks after operation (case 131). In the five cases (cases 123, 124, 127, 131 and 132) in which an opportunity was afforded to determine the urobilinogen value a relatively long time after splenectomy the amount was normal in four cases and slightly increased in one (case 127). In the case of acquired hemolytic jaundice in which splenectomy was performed considerable clinical improvement occurred at once; however, a much longer period intervened after splenectomy before the urobilinogen value for the feces had returned to a high normal level.

The results obtained with the qualitative van den Bergh reaction in this investigation agree with those of Andrewes,[32] who stated as his conclusion that the value of the method is chiefly in distinguishing frankly hemolytic from frankly obstructive jaundice. Biphasic reactions are seen to be of most frequent occurrence, but determination as to whether biphasic reaction is prompt or delayed has proved of no value in distinguishing the forms of jaundice. It should be added that a purely delayed reaction cannot be considered as characteristic of hemolytic jaundice alone, since it was encountered in occasional instances of jaundice of mild degree due to stone (cases 6, 17 and 27).

SUMMARY AND CONCLUSIONS

One hundred and thirty-five instances of jaundice or hepatic disease have been investigated with reference to the per diem excretion of urobilinogen in the urine and feces. The results justify the following conclusions:

Jaundice due to stone is not accompanied with a considerable increase in the amount of urobilinogen in the urine unless complications are

31. Goldschmidt, S.; Pepper, O. H. P., and Pearce, R. M.: Metabolism Studies Before and After Splenectomy in Congenital Hemolytic Icterus, Arch. Int. Med. **16**:437 (Sept.) 1915.

32. Andrewes, C. H.: A Clinical Study of van den Bergh's Test in Jaundice, Quart. J. Med. **18**:19, 1924.

present, such as acute cholecystitis or cholangeitis, biliary cirrhosis incident to persistent biliary obstruction or severe anemia. These complications are accompanied with at least a relatively marked increase, the actual amount of urobilinogen appearing in the urine being dependent to some extent on the degree of biliary obstruction and the consequent amount of urobilinogen formed in the bowel and reabsorbed from it.

With one exception jaundice due to stone and diffuse hepatic disease in this investigation was not accompanied with complete obstruction to the outflow of bile or complete cessation of the bile flow, such as is characterized by the presence of less than 5 mg. of urobilinogen per day in the feces, with slight or no traces in the urine. On the other hand, this has been the regular finding in cases of jaundice due to neoplasm. In only one instance in this group, an unusual melanomatous metastasis in the common duct, was the urobilinogen content of the feces more than 5 mg. per day, while the lowest value encountered in the former groups was 8.1 mg. per day, the amounts as a rule exceeding 10 mg.

Diffuse hepatic disease is usually characterized by a marked increase of urobilinogen in the urine; some of the instances of idiopathic diseases of the liver in the group of patients with cirrhosis were accompanied with evidence of an increased destruction of blood, i. e., an increase of the urobilinogen content of the feces and regenerative anemia, often macrocytic.

In hemolytic jaundice increases in the amount of urinary urobilinogen could not be correlated with increased destruction of blood, but for the most part it occurred when other factors, which are believed to disturb the function of the liver, also were present. The urobilinogen content of the feces was usually increased to a marked degree, in the majority of cases decreasing rapidly after splenectomy.

CLINICAL SIGNIFICANCE OF THE CREATINE RESERVE OF THE HUMAN HEART

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AND
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The first reported estimations of the creatine content of human cardiac muscle seem to be those of Constabel,[1] who analyzed a total of 38 hearts and obtained values ranging from 60 to 188 mg. per hundred grams for the concentration in the left ventricle. No relation to age or sex was observed, but hearts with fatty and other degenerative changes showed significantly lower values than those that were more nearly normal. In general the creatine concentration was about 10 per cent lower in the right than in the left ventricle.

In 1929 Bodansky, Schwab and Brindley[2] reported analyses of various muscles, including the myocardium of the left ventricle of a patient with generalized myositis fibrosa. The heart, which microscopically revealed certain abnormalities, such as enlargement of the fibers, granular cytoplasm, mononuclear inflammatory cells and increased fibrosis, contained 159 mg. of creatine per hundred grams of tissue. There were no data with which to compare this result but Constabel's, which were considered low. At the first opportunity, therefore, hearts were obtained from three healthy young adults who had met death by accident, autopsy being performed less than an hour post mortem. Analysis by the method of Rose, Helmer and Chanutin[3] gave values for creatine of 261, 257 and 220 mg., respectively (Bodansky[4]).

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1. Constabel, F.: Ueber den Kreatingehalt des menschlichen Herzmuskels bei verschiedenen Krankheitszuständen, Biochem. Ztschr. **122**:152, 1921.

2. Bodansky, M.; Schwab, E. H., and Brindley, P.: Creatine Metabolism in a Case of Generalized Myositis Fibrosa, J. Biol. Chem. **85**:307, 1929. Schwab, E. H.; Brindley, P.; Bodansky, M., and Harris, T. H.: Generalized Myositis Fibrosa, Ann. Int. Med. **6**:422, 1932.

3. Rose, W. C.; Helmer, O. M., and Chanutin, A.: A Modified Method for the Estimation of Total Creatinine in Small Amounts of Tissue, J. Biol. Chem. **75**:543, 1927.

4. Bodansky, M.: Creatine in Human Muscle, J. Biol. Chem. **91**:147, 1931.

From these meager references [5] it is apparent that little attention was given to the subject as long as creatine was known merely as a constituent of muscle without a well defined physiologic rôle. However, interest was soon aroused as the result of a succession of important discoveries which showed, first, that a considerable proportion of the creatine exists in muscle as an ester of phosphoric acid (Eggleton and Eggleton [6] and Fiske and Subbarow [7]), that the energy for muscular contraction is primarily derived from the hydrolysis of phosphocreatine (Lundsgaard [8]) and that within certain limits the newer concepts of the chemistry of muscle activity, based partly on these discoveries, could be applied to the metabolism of cardiac muscle (Clark, Eggleton and Eggleton [9]).

For obvious reasons a complete study of the relation of the creatine content to the metabolism of cardiac muscle in health and disease on human material is out of the question. The rapid hydrolysis and disappearance of glycogen and phosphocreatine which result from even slight alterations of the in vivo conditions preclude their estimation after death; hence those who have attempted to study the problem in man have confined themselves to the determination of the total creatine content, the two notable contributions along this line being those of Cowan [10] and Seecof, Linegar and Myers.[11]

Cowan [10] reported analyses of 80 hearts, 48 of which were classified as normal, as they showed comparatively little change anatomically (cloudy swelling, brown atrophy and sclerosis). Death was due to a variety of causes, such as pneumonia, empyema, tuberculosis, carcinoma, anemia and diabetes. The average creatine concentration was 202 mg. per hundred grams of tissue, with a standard deviation of 37 mg. Evidence of cardiac decompensation existed in 17 cases. In these the average was 147 mg., with a standard deviation of 37 mg. In a third

5. Constabel.[1] Bodansky, Schwab and Brindley.[2] Bodansky.[4]

6. Eggleton, P., and Eggleton, G. P.: The Inorganic Phosphate and a Labile Form of Organic Phosphate in the Gastrocnemius of the Frog, Biochem. J. **21**: 190, 1927.

7. Fiske, C. H., and Subbarow, Y.: The Nature of the "Inorganic Phosphate" in Voluntary Muscle, Science **65**:401, 1927; Phosphocreatine, J. Biol. Chem. **81**: 629, 1929.

8. Lundsgaard, E.: Untersuchungen über Muskelkontraktionen ohne Milchsäurebildung, Biochem. Ztschr. **217**:162, 1930.

9. Clark, A. J.; Eggleton, M. G., and Eggleton, P.: Phosphagen in the Perfused Heart of the Frog, J. Physiol. **75**:332, 1932.

10. Cowan, D. W.: The Creatine Content of the Myocardium of Normal and Abnormal Human Hearts, Am. Heart J. **9**:378, 1934.

11. Seecof, D. P.; Linegar, C. R., and Myers, V. C.: The Difference in Creatine Concentration of the Left and Right Ventricular Cardiac Muscles, Arch. Int. Med. **53**:574 (April) 1934.

group of 15 hearts of subjects who had shown clinical manifestations of heart disease and pathologic evidence of myocardial damage, cardiac hypertrophy or some other disorder, the creatine concentration of the left ventricle averaged 165 mg., with a standard deviation of 30 mg. According to Cowan,[10] his results suggested that the "reserve" of the heart closely parallels its creatine content.

Seecof, Linegar and Myers [11] compared the creatine concentrations of the left and right ventricles. They analyzed a total of 102 hearts, employing in each case blocks of tissue from anatomically similar locations. In 84 the range for the left ventricle was from 116 to 369 mg. (average, 211 mg.). The range for the right ventricle was from 93 to 283 mg. (average, 148 mg.). Except in the heart of a newborn infant, the concentration was invariably greater in the left than in the right ventricle, the average difference being 63 mg., or 30 per cent, using the left ventricle as the standard.

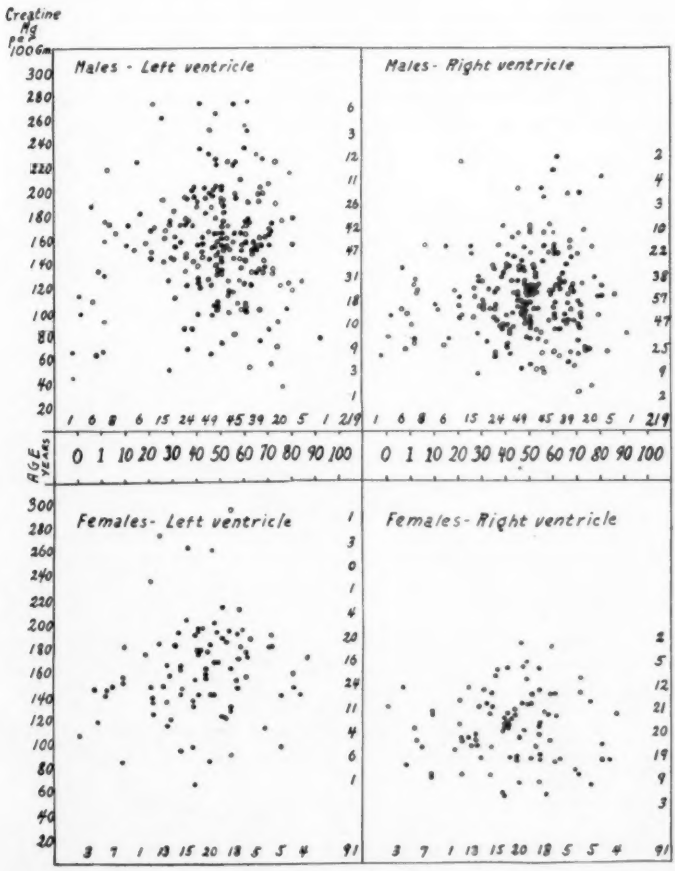
The present report is based on the analyses of the left and right ventricles of 310 hearts, the largest series so far reported.[12] In addition, data have been obtained for the papillary muscles of 52 hearts. The cardiac samples were taken from approximately identical locations, in accordance with the suggestion of Seecof, Linegar and Myers.[11] Most autopsies in this institution are performed within four or five hours after death, seldom later than twenty-four hours. In the interval the corpse is kept in a morgue maintained at 3 or 4 C. For this investigation analyses were not made when the autopsy was unduly delayed. Usually the tissues were promptly subjected to the preliminary stages of analysis, but occasionally a delay of several hours was unavoidable, during which time the specimens were kept in stoppered bottles in a refrigerator. Our experience has confirmed the observations of others that aseptic autolysis of short duration has no significant effect on the total creatine content of tissues. For the estimation of creatine the method of Rose, Helmer and Chanutin [3] was used, every detail of the procedure being carefully controlled.[13]

12. After approximately half this work was completed Herrmann and his co-workers independently analyzed a number of left ventricles, some of which were in our series of autopsies. Their results were included in a discussion entitled "Some Biochemical Factors of Heart Failure" (South. M. J. **29**:386, 1936).

13. In connection with various studies in this laboratory [17] a large number of creatine estimations have been made for a relatively uniform statistical population (normal rats, heart and other tissues). For over two years the practice has been to carry out the analyses of the human hearts in company with a sufficient number of tissues of normal rats, especially cardiac tissue, so that any significant technical error in any set of determinations would be readily detected.

RESULTS

In evaluating the results it is to be realized that the 310 hearts represent a heterogeneous and complex statistical population, but in order to present a general view of the data and their variability and


Creatine Mg per 100 Gm
Males - Left ventricle
Males - Right ventricle
Females - Left ventricle
Females - Right ventricle
AGE YEARS
0 1 10 20 30 40 50 60 70 80 90 100

Creatine concentrations of the left and of the right ventricle, arranged according to the age and sex of the subjects. The white circles represent white subjects and the black circles Negroes. The numbers for each age group are given along the abscissa; the numbers along the ordinate indicate the distribution of cases for each interval of 20 mg. in creatine concentration.

to bring out grossly the relation of the right to the left ventricle and such other differences as may conceivably be related to age, sex and race, the data for the group as a whole are represented in the accom-

panying figure. Ten of the 310 hearts were of new-born infants or of infants less than 1 year old. These will be considered separately. The remaining 300 hearts were of subjects whose ages ranged from 1 to 92 years. In these the creatine concentration varied from a minimum of 38 to a maximum of 295 mg., the average being 159.2 mg. The concentration in the right ventricle likewise varied within wide limits, from 38 to 230 mg. with an average of 114 mg.

TABLE 1.—*Creatine Concentration of the Heart*

	Mg. of Creatine per 100 Gm. of Tissue			Standard Deviation
	Maximum	Minimum	Average	
212 males				
Left ventricle	275	38	157.10	45.56
Right ventricle	230	38	114.40	34.71
Difference and standard error of the difference of the two means	...	..	42.7 ± 3.00	
P (Fisher [14])	...	..	<0.01	
88 females				
Left ventricle	295	67	163.80	40.11
Right ventricle	184	58	114.60	28.46
Difference and standard error of the difference of the two means	...	..	49.2 ± 5.20	
P (Fisher [14])	...	..	<0.01	

TABLE 2.—*Classification of Patients*

Group		Number of Patients		Conditions Included
		Male	Female	
1	Congestive heart failure	50	20	
2	Cardiac hypertrophy (>400 Gm. in males; >350 Gm. in females)	39	16	Syphilitic aortitis, hypertension, subacute bacterial endocarditis, chronic nephritis, cerebral hemorrhage, etc.
3	Clinical or pathologic evidence of heart disease; moderate to severe degeneration of myocardium, not included in groups 1 and 2	51	27	Pericarditis, chronic nephritis, peritonitis, tuberculosis, diabetes, carcinoma, pellagra, pneumonia, diphtheritic myocarditis, etc.
4	No evidence of heart disease; minimal degenerative changes of myocardium	40	15	Meningitis, tuberculosis, carcinoma, nephritis, eclampsia, peritonitis, suicide, etc.
	Total	180	78	

Of the 300 subjects over 1 year of age, 212 were males and 88 females. Although there appeared to be little difference between the averages for the two sexes, nevertheless, the data for each group were tabulated separately (table 1). The results were further arranged according to the predominant clinical and pathologic observations. Thus 50 males definitely died of congestive heart failure; in 39 there was marked cardiac hypertrophy. For reference a summary of the four subdivisions is given in table 2, while the data for each group are outlined in table 3. In these tabulations only those cases were included in

which both the clinical and the pathologic data were essentially complete. Borderline cases, or cases in which the information was incomplete or uncertain, were omitted from these tables.

TABLE 3.—*Creatine Reserve of Myocardium and Comparison of Left and Right Ventricles in Various Groups*

	Mg. of Creatine per 100 Gm. of Tissue			Standard Deviation
	Maximum	Minimum	Average	
Group 1 (congestive heart failure)*				
30 males				
Left ventricle	265	38	139.1	53.86
Right ventricle	218	38	103.0	35.38
Difference	...	..	36.1 ± 9.1	
P (Fisher [14])	...	..	<0.01	
20 females				
Left ventricle	295	51	146.1	53.57
Right ventricle	169	49	108.0	35.11
Difference	...	..	38.1 ± 14.3	
P (Fisher [14])	...	..	<0.01	
Group 2 (cardiac hypertrophy)				
39 males				
Left ventricle	237	81	145.6	34.80
Right ventricle	169	49	109.0	22.70
Difference	...	..	36.6 ± 6.6	
P (Fisher [14])	...	..	<0.01	
16 females				
Left ventricle	260	90	167.0	41.40
Right ventricle	184	69	111.0	31.06
Difference	...	..	56.0 ± 12.9	
P (Fisher [14])	...	..	<0.01	
Group 3				
51 males				
Left ventricle	265	58	165.0	47.50
Right ventricle	223	62	116.0	37.90
Difference	...	..	49.0 ± 8.5	
P (Fisher [14])	...	..	<0.01	
27 females				
Left ventricle	264	98	168.0	35.50
Right ventricle	160	59	113.0	25.10
Difference	...	..	55.0 ± 8.4	
P (Fisher [14])	...	..	<0.01	
Group 4				
40 males				
Left ventricle	273	97	174.7	29.60
Right ventricle	212	84	127.8	20.10
Difference	...	..	46.9 ± 6.5	
P (Fisher [14])	...	...	<0.01	
15 females				
Left ventricle	236	140	171.3	28.60
Right ventricle	162	87	123.7	23.30
Difference	...	..	47.6 ± 9.4	
P (Fisher [14])	...	..	<0.01	

* Heart weights in grams: group 1, males, minimum 280, maximum 1,060, average 546.5; females, minimum 330, maximum 720, average 499. Group 2, males, minimum 400, maximum 680, average 480; females, minimum 350, maximum 600, average 423.

From the data in tables 1 and 3 it will be noted that the creatine concentrations of both ventricles varied within wide limits, the variability being greatest for the group of subjects with congestive heart failure and least for the group in which there was no evidence of heart dis-

ease. In the group with heart failure the average concentrations for the two ventricles were lower than the corresponding values for the entire population and especially for groups 3 and 4. As a rule the concentration was greater in the left than in the right ventricle, as shown by the difference between their means. Indeed, the probability that these differences were not due to chance exceeds 100:1 ($P = < 0.01$) for all groups. While this may be taken to predict the probable outcome for any comparable series of analyses, it should not be assumed that the result in any given case can be predicted with any confidence, for even among adults there were frequent exceptions to the rule of proportionality for the creatine content of the two ventricles (table 6).

The concentration in the left ventricle was somewhat higher for the females than for the males. However, the difference cannot be regarded as statistically significant ($t = 1.17$, $P = 0.2$ or 0.3). In about two

TABLE 4.—*Distribution of Concentrations of Creatine in the Left Ventricle Above 200 Mg. and Below 120 Mg.*

Creatine Concentration, Mg. per 100 Gm.	Total Number of Cases	Group 1	Group 2	Group 3	Group 4	Unclassified
260-295	11	2	1	5	3	0
240-259	2	0	1	1	0	0
220-239	13	2	3	4	3	1
200-219	15	2	1	4	7	1
Totals	41	6	6	14	13	2
100-119	18	10	6	2	0	0
80-99	15	5	5	4	1	0
60-79	8	7	0	1	0	0
Below 60	4	3	0	1	0	0
Totals	45	25	11	8	1	0

thirds of the cases the creatine concentrations for the left ventricles were within the limits 159.2 ± 33.7 mg. There were indeed only 41 cases in which the concentration exceeded 200 mg. and 45 in which it was less than 120 mg. Classification of these results according to the predominant clinical and pathologic observations (table 4) revealed the following interesting facts: Of the 41 subjects who showed a concentration greater than 200 mg., only 6 belonged to group 1 and 6 to group 2. The greater number represented subjects belonging to groups 3 and 4. On the other hand, of the 45 persons in whom the creatine concentration was low (120 mg. or less), 36 were in groups 1 and 2 and only 9 in groups 3 and 4. These findings may be considered as partly supporting Cowan's suggestion that the functional reserve of the heart is related to its creatine reserve. However, a more critical analysis of the data from this standpoint will be attempted shortly.

L/R Ratio.—In table 5 are given the ratios of the creatine concentration for the left (L) and the right (R) ventricle. It will be observed

that for the males the average L/R values were somewhat lower in groups 1 and 2 than in group 4, while in group 3 the ratio was highest. This may be due to the fact that the last group included a considerable proportion of subjects with pneumonia, in which there was often present moderate or severe degeneration of the myocardium, the classification in group 3 being based on this finding. Moreover, in pneumonia, as will be seen, the creatine concentration of the right ventricle tends to be lowered. In the females cardiac hypertrophy (group 2) was much less often associated with creatine depletion from the left ventricle than in males. This point will be referred to again later.

For the 212 males the average difference between the two ventricles was 43 mg. (maximum, + 134; minimum, — 27 mg.). The L/R ratios averaged 1.38 (maximum, 2.87; minimum, 0.73), with a standard deviation of 0.35. For the 88 females the average difference between the ventricles was 46.5 mg. (maximum, + 186; minimum, + 6 mg.). The

TABLE 5.—*Ratios of Creatine Concentration in Left and Right Ventricles (L/R)*

Group	Male		Female	
	Number of Cases	L/R (Average)	Number of Cases	L/R (Average)
1	50	1.35	20	1.35
2	39	1.34	16	1.50
3	51	1.42	27	1.49
4	40	1.37	15	1.38
Total*	212	1.38	88	1.43

* This comprises all the autopsies on adults and includes a number of cases not classified in the four groups.

L/R ratios averaged 1.43 (maximum, 2.7; minimum, 1.05), with a standard deviation of 0.336. As these figures showed striking variability, it seemed of interest to inquire whether the more divergent results were in any way associated with definite clinical or pathologic manifestations. Accordingly the results were classified as in table 6, grouping on the one hand those cases in which the L/R ratios exceeded 1.6 (i. e., in which there was a relative impoverishment of the myocardium of the right ventricle) and, on the other hand, those cases in which the L/R ratio fell below 1.1 (i. e., in which there was relative creatine impoverishment of the left ventricle). Since we had observed low creatine values for the right ventricle in cases of lobar pneumonia and other types of severe pulmonary involvement, cases of these conditions are grouped separately in the table, except when the figures are enclosed in parentheses. From table 6 it will be noted that in 31 of the 69 cases in which there was a relative loss of creatine from the right ventricle there was pneumonia or other severe involvement of the lungs (tuberculous pneumonia, conglomerate tuberculosis or severe pulmonary edema). As there were a total of 67 cases in which a com-

parable degree of pulmonary involvement was present, it follows that in 46 per cent of these there occurred a relative loss of creatine from the right ventricle. This is to be compared with 12 per cent, representing a similar relation in the remaining 233 cases. From these data, which are admittedly meager, it seems that in persons with pneumonia and to some extent in other types of severe pulmonary disease a lowered creatine reserve in the right ventricle occurred about four times as often as in the remaining autopsy population. It may be further observed that in 7 of 12 cases in which death was due to lobar pneumonia the L/R ratio exceeded 1.6; this occurred in 10 of 28 cases of bronchopneumonia.

A lowered creatine reserve in the right rather than in the left ventricle is not an uncommon finding in cases of congestive heart failure.

TABLE 6.—*Distribution of L/R Ratios Above 1.6 and Below 1.1*

Concentration of Creatine: Left Ventricle / Right Ventricle	Number of Cases	Group 1	Group 2	Group 3	Group 4	Pneumonia	Other Severe Pulmonary Conditions
Above 2.6	3	1	0	0	0	1	1
2.4-2.59	5	0	0	0	0	5	0
2.2-2.39	3	0	0	1	0	1	1
2.0-2.19	5	1	0	0	1	2	1
1.8-1.99	20	5	2	4	3	5	1
1.6-1.79	33	6	5	7	2	10	3
Total	69	13	7	12	6	24	7
1.0-1.09	21	14	3	2	2	(1)	0
0.8-0.99	12	8	1	2	1	(1)	0
0.73-0.79	2	1	0	1	0	0	0
Total	35	23	4	5	3	(2)	0

Indeed, in 13 of a total of 70 patients (50 males and 20 females) this was noted. More often, however, the L/R ratio tends to be low (relative depletion of creatine from the left ventricle), as indicated in table 6. Of the 35 cases in which the L/R ratio was less than 1.1, 23 were in group 1 (congestive heart failure). Only 2 of the 35 subjects had pneumonia (lobar), both being classified in group 3 on the basis of the microscopic picture.

The results therefore indicate that such factors as may be expected to contribute to strain or exhaustion of either the left or the right ventricle are often associated with a lowered creatine concentration of the corresponding portion of the myocardium. A more adequate appreciation of the constancy and significance of the changes may be gained, however, from the data outlined in table 7. In this table are given the values of the probabilities of the nonsignificance of the difference of the means, these having been calculated for each set of pairs. This table thus affords a ready means of comparing the average myocardial creatine reserve of any group with that of any other.

To illustrate, in the case of the left ventricle (males), comparison of group 1 (congestive heart failure) with group 2 (cardiac hypertrophy, compensated heart disease and other disorders) gives the value of 0.5 for P, which denotes that no real significance can be attached to the differences between the means for these groups (see also table 3); nor can the value 0.05 obtained on comparing groups 1 and 3 and 2 and 3 (left ventricle, male) be considered of statistical significance, even though it represents a 20:1 probability that the differences were not due to chance. On the other hand, the P value of 0.02 (50:1 probability) derived from the means for group 1 and the total male population may be accepted as significant, as may certainly the values of <0.01 in columns 5 and 9. From these it is apparent that there was definitely a significant difference between the mean concentrations of creatine of the subjects with heart failure and those without heart disease (group 4) and that there was also a real difference between the latter

TABLE 7.—*Comparison of Various Groups, as Shown by the Values of P* *

	Males								Females							
	Left				Right				Left				Right			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Total	**0.02**	0.2	0.4	0.20	0.05	0.4	0.7	0.90	0.1	0.8	0.7	0.5	0.4	0.7	0.8	0.3
1	....	0.5	0.05	**<0.01**	....	0.4	0.05	**<0.01**	...	0.2	0.1	0.1	...	0.8	0.6	0.2
2	....	...	0.05	**<0.01**	....	...	0.4	**<0.01**	...	...	>0.9	0.4	...	...	0.9	0.4
3	....	...	....	0.3	....	...	...	0.1	...	...	...	0.8	...	...	...	0.2

* For an explanation of the use of the letter P here see text.

and those with cardiac hypertrophy (group 2). But, as has been stressed in discussing the differences between the left and the right ventricle, these calculations, while predicting the probable results in similar comparisons, do not necessarily determine with any degree of assurance the outcome in any single case, as it is not uncommon, even in congestive heart failure, for the creatine reserve of the myocardium to remain unchanged or even at levels well above the average.

The data in table 7 suggest, moreover, a difference between males and females. It will be observed that the values of P derived from the comparisons of group 1 with the total female population and with group 4 denote only a 10:1 probability that the differences between the means were not due to chance. Even less significant differences are indicated by the values of P based on the following comparisons: left ventricle, groups 2 and 4, and 3 and 4; right ventricle, all combinations. However, this disparity between the sexes may be more apparent than real. Because of the wide range of variability (note the standard deviations for group 1, male and female, table 3) a greater number of females may have yielded value for P comparable to those obtained for the males. When the variation of individual observations is small,

a small group of observations may suffice, and indeed it is because Fisher's calculations [14] may be applied to small numbers of experiments or observations that they have found such general use.

In cardiac hypertrophy the creatine concentration of the left ventricle was comparatively higher in females than in males (table 3). Although there was a greater incidence of syphilitic aortic disease in the males, while in the females there was a greater proportion of hypertensive heart disease, no definite correlation was possible between these factors and the creatine reserve of the myocardium; nor was it possible to establish any relation, either in group 2 or in group 1, with regard to therapeutic management (digitalis, various diuretics and other drugs) or to the administration terminally of dextrose, epinephrine, caffeine sodiobenzoate and other drugs. In the absence of definite correlations, the suggestion is offered tentatively that the lower creatine concentration of the myocardium for the males in group 2 as compared with that of the females in group 2 may be related not to heart disease primarily but to other associated or superimposed factors. Thus the added strain on the heart due to physical work may conceivably be responsible, in part, for the more frequent reduction of the myocardial reserve of creatine in men with heart disease than in women. In this connection it is relevant to refer to the recent observation of Chanutin and Ludewig [15] that in cardiac hypertrophy produced in partially nephrectomized hypertensive rats, the creatine content increases in approximately direct proportion as the size of the heart increases; hence the creatine concentration remains fairly constant.

Papillary Muscles.—In 52 analyses the following results were obtained:

	Mg. of Creatine per 100 Gm.		
	Maximum	Minimum	Average
Left ventricle	272	104	167.0
Right ventricle	223	52	115.3
Papillary muscle (left ventricle)	208	85	139.4

The creatine concentrations of the papillary muscles appeared to be intermediate between the concentrations in the two ventricles. In fact, this relation held in 43 of the 52 hearts analyzed. In 2 cases the concentrations were somewhat greater than that in the left ventricle, while in 7 it was less than that in the myocardium of the right ventricle. The concentration of creatine in the papillary muscle obtained from the right side was usually less than that from the left side.

14. Fisher, R. A.: Statistical Methods for Research Workers, ed. 4, Edinburgh, Oliver & Boyd, 1932.

15. Chanutin, A., and Ludewig, S.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: IV. Creatine Content of Hypertensive Hypertrophied Hearts of Rats Fed Whole Dried Meat, Arch. Int. Med. **57**:887 (May) 1936.

Creatine Concentration of the Heart in Infancy.—In the newborn somewhat lower values were obtained than in the case reported by Seecof, Linegar and Myers.[11] In agreement with their observation the concentration was lower in the left than in the right ventricle.

	Mg. of Creatine per 100 Gm.	
	Left	Right
5 to 6 month fetus	45	66
Female new-born	108	131
Male new-born	78	112

In a 7 week old infant the relation of the concentrations was 98/97. In 6 others who died during the first year of life the creatine concentrations varied from 62 to 189 mg. in the left ventricle and from 69 to 146 mg. in the right. The L/R ratio in 1 infant was 1; in 4 others it exceeded 1; in a child with bronchopneumonia it was 133/69 = 1.9.

COMMENT

Without unnecessarily belaboring the subject, it may be stated briefly that cardiac activity depends on an adequate supply of oxygen and sufficient reserves of glycogen, phosphocreatine and such other components as may participate in the energy transformations of the myocardium. The relative sensitivity of the heart to oxygen want, its low ability, compared to skeletal muscle, to acquire an oxygen debt and the tendency to a rapid loss of glycogen and an increase in the amount of lactic acid which accompanies anoxemia, from whatever cause, have been established by recent investigations.[16] This leaves little doubt that in considering the problems of circulatory failure the biochemical aspects loom large and cannot be neglected. At the same time it may be appropriate to stress that the conditions associated with heart failure, clinically, may be sufficiently different from those in the experimental animal to render uncertain such assumptions as may be based entirely on experimental data.

The specific point in question is the relation of heart failure to the creatine reserve of the myocardium. As has been shown previously,[17]

16. Katz, L. N., and Long, C. N. H.: Lactic Acid in Mammalian Cardiac Muscle, Proc. Roy. Soc., London, s.B **99**:8, 1926. Hines, H. J. G.; Katz, L. N., and Long, C. N. H.: ibid. **99**:20, 1926. Katz, L. N.; Kerridge, P. T., and Long, C. N. H.: ibid. **99**:26, 1926. Himwich, H. E.; Goldfarb, W., and Nahum, L. H.: Changes of the Carbohydrate Metabolism of the Heart Following Coronary Occlusion, Am. J. Physiol. **109**:403, 1934. Meakins, J. C.: Modern Muscle Physiology and Circulatory Failure, Ann. Int. Med. **6**:506, 1932.

17. Bodansky, M.: The Effect of Thyroid and Thyroxine on the Concentration of Creatine in the Heart, Muscle, Liver, and Testes of the Albino Rat, J. Biol. Chem. **109**:615, 1935. Bodansky, M.; Pilcher, J. F., and Duff, V. B.: J. Exper. Med. **63**:523, 1936. Bodansky, M., and Duff, V. B.: Proc. Soc. Exper. Biol. & Med. **34**:307, 1936; Endocrinology **20**:537 and 541, 1936.

heart failure in the hyperthyroid rat is associated with a marked reduction of the creatine concentration of the myocardium. From an initial value of about 190 mg., which closely approximates the normal concentration in man, the creatine concentration may be reduced to 90 mg., but rarely below this level, because circulatory failure usually supervenes when the creatine reserve has been reduced to about 50 per cent of normal. Not only are the results such as to justify a prediction of the probable outcome for any similar series of experiments, but because of their relative uniformity a significant loss of creatine may be predicted with reasonable confidence for any single experiment, there having been essentially no exceptions to the rule among more than 300 rats treated with large doses of thyroid or thyroxin. This stands in marked contrast to the results in cases of clinical heart failure described in the present paper. While the values for P reveal significant differences between the means of certain groups (subjects with heart failure compared with the entire population or with the subjects in whom there was no evidence of heart disease), individual results lacked uniformity and were hence unpredictable. In short, each case of heart failure seems to be a law unto itself. The conditions clinically are apparently too complex to permit the ready and simple definition that may be justified in experimental heart failure, in which, on the basis of our work and the work of others, it seems that the glycogen and phosphocreatine mechanisms are primarily affected and that the depletion of creatine follows the loss of phosphocreatine. Available information and the examination of our own clinical data in relation to therapeutic measures and other factors do not permit an explanation of the diversity of the results in heart failure, the maintenance of the creatine reserve at a comparatively high level in some cases and its reduction in others. It does appear, however, that such factors as may be expected to increase the load on either the right or the left ventricle, thereby leading to exhaustion, are often associated with a lowered creatine reserve of the corresponding portion of the myocardium.

SUMMARY

Determinations have been made of the creatine concentration of the right and of the left ventricle of 310 hearts obtained at autopsy. In addition, the papillary muscles of 52 hearts were analyzed.

The data have been treated statistically and correlated, as far as possible, with the clinical manifestations and pathologic observations.

TREATMENT OF ESSENTIAL AND MALIGNANT HYPERTENSION BY SECTION OF ANTERIOR NERVE ROOTS

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Since no medical treatment is known which will lower the level of the blood pressure of a patient suffering from essential hypertension more than temporarily, surgical measures deserve trial. That it is desirable to reduce the level of the blood pressure in such a patient has not always been conceded. Clinical observation, however, suggests that continued hypertension of itself causes vascular disease. Temporary reduction of an abnormally high pressure by means of drugs, such as sodium thiocyanate or colloidal sulfur, has not been observed in this clinic to produce symptoms and signs of inadequate gaseous metabolism or disturbances of tissue nutrition. These might have been expected were hypertension a compensatory mechanism serving some useful purpose. Nor have recent observations [1] supported the belief of Traube that the arterial pressure must be abnormally elevated to maintain an adequate perfusion of blood through the kidneys. Reduction, especially of the diastolic pressure, might conceivably interfere with the blood supply of the heart in cases of coronary sclerosis and so predispose to attacks of angina pectoris. This has not been observed so far as we are aware. It appears that no contraindications have been established, though they may well exist, for reduction of the arterial pressure of patients suffering from essential hypertension. The purpose of section of the anterior nerve roots is, then, to reduce the abnormal pressure by removing partially the nervous control of a portion of the splanchnic area, including the abdominal wall.

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1. Page, I. H.: The Effect on Renal Efficiency of Lowering Arterial Blood Pressure in Cases of Essential Hypertension and Nephritis, J. Clin. Investigation **13**:909, 1934.

POSSIBLE MECHANISM OF THE LOWERING OF BLOOD PRESSURE BY SECTION OF THE ANTERIOR ROOTS

It has long been recognized among physiologists that the vessels of the splanchnic region are of importance in the maintenance of the blood pressure level. The evidence for this belief is varied. Closure of the aorta below the level of the renal vessels produces only a slight rise in the blood pressure. The pressure is elevated slightly more if the subclavian and carotid arteries are simultaneously closed. If, however, the aorta is clamped directly above the diaphragm, eliminating the splanchnic region from the circulation, a marked rise in pressure occurs (von Bezold,[2] Ludwig and Thiry[3]). In 1875 Litten[4] noted that ligature of the superior mesenteric artery of the dog resulted in a prompt rise in the arterial pressure, which frequently persisted for several hours. Longcope and McClintock[5] observed in their experiments that hypertension resulted when the superior mesenteric artery and the celiac axis were constricted. Permanent hypertension was not obtained, probably owing to the development of collateral circulation. Von Bezold[2] showed that in curarized rabbits electrical stimulation of isolated segments of the cord resulted in a rise in the blood pressure, the extent varying with the segment stimulated. Stimulation of segments in the cervical region was without effect, but below the third thoracic segment both the heart rate and the arterial pressure were markedly increased. Bradford[6] stimulated the anterior nerve roots in dogs within the dura and found that while the fourth and fifth thoracic and third lumbar roots had only slight power to elevate the blood pressure and constrict the kidneys (measured by an oncometer), the roots included between these limits were highly effective. Stimulation of the tenth and thirteenth thoracic roots caused especially powerful constriction of the kidneys. Bradford found that the area from which the renal vessels are supplied is extensive and apparently coextensive with that supplying the abdominal vessels. It was thus shown that the splanchnic region is important in the regulation of the arterial pressure and that

2. von Bezold, A.: Untersuchungen über die Innervation des Herzens, Leipzig, W. Engelmann, 1863.

3. Ludwig, C., and Thiry, L.: Ueber den Einfluss des Halsmarkes auf dem Blutstrom, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **49**:421, 1864.

4. Litten, M.: Ueber die Folgen des Verschlusses der Arteria mesaraica superior, Arch. f. path. Anat. **63**:289, 1875.

5. Longcope, W. T., and McClintock, A. T.: The Effect of Compression of the Superior Mesenteric Artery upon the Systemic Blood Pressure, Univ. Pennsylvania M. Bull. **22**:226, 1909. The Effect of Permanent Constriction of the Splanchnic Arteries and the Association of Cardiac Hypertrophy with Arteriosclerosis, Arch. Int. Med. **6**:439, 1910.

6. Bradford, J. Rose: The Innervation of the Renal Blood Vessels, J. Physiol. **10**:358, 1889.

the nervous control of this region lies in the anterior nerve roots issuing from the cord between the third thoracic and the third lumbar segment.

The experiments of Burch, Harrison and Blalock [7] may be taken as indicating the practical importance of this fact. They showed that susceptibility to hemorrhage was only slightly greater in dogs receiving ether than in control unanesthetized animals, but severe circulatory failure and death were produced by the removal of relatively small amounts of blood from animals under spinal anesthesia. The difference was attributed to the fact that the normal dogs and those receiving ether responded to hemorrhage by a compensatory vasoconstriction which tended to maintain the blood pressure, while this constrictor response was diminished or abolished by spinal anesthesia, and therefore a relatively slight decrease in the volume of the blood caused a disproportionately large decline in the pressure.

Cyon and Ludwig [8] and Bever and Bezold [9] recognized the importance of the control of the abdominal vessels by the splanchnic nerves. Cutting one of them in curarized or lightly anesthetized rabbits resulted in a fall in pressure of from 30 to 50 mm. of mercury, and section of the second one produced a further fall of from 8 to 10 mm. of mercury (Cyon and Ludwig). Bever and Bezold observed practically the same lowering of pressure after section of both splanchnic nerves within the thorax as after division of the spinal cord in the cervical region. Stimulation of the distal portion of the severed nerve resulted in marked elevation of the blood pressure, which was lacking when the central end was stimulated (Cyon and Ludwig).

Recovery of the tone of the vessels in normal animals after denervation appears to be a general phenomenon (Grant, Camp, Graybiel and Rothschild [10] and Wilson, Roome and Grimson [11]). Whether the abnor-

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8. Cyon, E., and Ludwig, C.: Die Reflexe eines der sensiblen Nerven des Herzen auf die motorischen der Blutgefässe, Arb. a. d. physiol. Anstalt zu Leipzig **1**:128, 1866.

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10. Grant, R. T.; Camp, P. D.; Graybiel, A., and Rothschild, P.: Further Observations on the Vessels and Nerves of the Rabbit's Ear, with Special Reference to the Effects of Denervation, Clin. Sc. **2**:1, 1935.

11. Wilson, H.; Roome, N. W., and Grimson, K.; Complete Sympathectomy: Observations on Certain Vascular Reactions During and After Complete Exclusion of the Sympathetic Nervous System in Dogs; an Experimental Study, Ann. Surg. **103**:498, 1936.

mal tone in hypertensive animals also is recovered is not known. The tone of the vessels is regained in from thirteen to twenty-five days after section of the splanchnic nerves in cats, and the blood pressure returns to normal (Magnus [12]). The rise in blood pressure which follows stimulation of the splanchnic nerves is believed to depend on two distinct mechanisms: (1) contraction of the peripheral vessels of the splanchnic area due directly to stimulation of the vasoconstrictor nerves supplying that region and (2) contraction of the peripheral vessels throughout the whole organism due to liberation of epinephrine as a result of the direct stimulation of the nerves to the adrenal glands (Anrep [13] and Lehndorff [14]).

Evidence of a different nature concerning the rôle of the splanchnic region as a regulator of the blood pressure has been furnished by Jansen, Tams and Achelis.[15] They found that in dogs closure of the large vessels to the head and extremities resulted in small and transient rises in the arterial pressure. Conversely, closure of the mesenteric artery resulted in marked and sustained rises, thus confirming the findings of Longcope and McClintock.[5] Preliminary closure of the mesenteric artery followed by closure of the vessels to the limbs produced a rise in pressure considerably greater than the sum of the elevations when the procedures were carried out separately. In a normal human being binding three extremities in elastic bandages, the blood pressure being measured in the fourth limb, caused only a temporary rise in the blood pressure, but in a hypertensive patient the rise was greater and prolonged. These observations are taken to mean that in a hypertensive patient the reservoir function of the abdominal vessels has been lost and can no longer compensate for an increase in the volume of blood. These investigators found, further, that cold colonic irrigations, which cause splanchnic vasoconstriction, produced a much greater rise in pressure than cold baths, which cause peripheral vasoconstriction.

That narrowing of the arteries of the extremities does not in itself cause hypertension was noted, among others, by Fishberg.[16] He

12 Magnus, R.: Ueber peripheren Gefässtonus im Splanchnicusgebiet, Arch. f. d. ges. Physiol. **115**:331, 1906.

13. von Anrep, G.: On the Part Played by the Suprarenals in the Normal Vascular Reactions of the Body, J. Physiol. **45**:307, 1912.

14. Lehndorff, A.: Ueber die Ursachen der typischen Schwankungen des allgemeinen Blutdruckes bei Reizung der Vasomotoren, Arch. f. Physiol., 1908, p. 362.

15. Jansen, W. H.; Tams, W., and Achelis, H.: Blutdruckstudien: I. Zur Dynamik des Blutdrucks (nach experimentellen Untersuchungen an Mensch und Tier), Deutsches Arch. f. klin. Med. **144**:1, 1924.

16. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1931, p. 193.

observed that the blood pressure was normal in a patient suffering from thrombo-angiitis obliterans in whom both legs were amputated and the left arm was severely involved. We have repeatedly noted in this clinic that the arterial pressure is unchanged in a hypertensive patient during attacks characterized by intense pallor of the skin of the fingers (so-called "dead fingers").

Steele and Kirk [17] have presented convincing evidence that the temperature of the skin of a patient with essential hypertension does not differ from that of a normal subject. Diurnal variations in the surface temperature regularly occur in hypertensive patients without any significant change in the arterial pressure. Elevation of the blood pressure evidently does not depend on constriction of the arterioles of the skin, though it may be accompanied with it.

This varied evidence is taken to mean that the splanchnic vessels constitute an important but not the only flexible reservoir which governs the level of the arterial pressure.

It is obvious from clinical observation that constriction of vessels must be present in cases of hypertension in regions other than the splanchnic region. For example, the arterioles in the retina can be seen to be markedly reduced in caliber. Recent important evidence of Prinzmetal and Wilson [18] and Pickering [19] indicated that, so far as conclusions can be drawn from the measurement of the blood flow in the forearm, increased vascular resistance is widespread throughout the body. Since an increase of the blood flow associated with inhibition of the vasoconstrictor impulses to the vessels of the forearm and hand by warming the body was no greater in a patient with hypertension than in a normal subject, it was concluded that the vascular hypertonus was not of vasomotor origin. Prinzmetal and Wilson found that sympathetic vasoconstriction is responsible for the hypertonus of coarctation of the aorta, but with this finding Pickering did not agree.

These results provide evidence that the nervous system plays an unimportant part in the genesis of hypertension. However, clinical observation makes it difficult to believe that it does not play an essential rôle, at least in early stages of certain types of hypertension. The marked fall in the arterial pressure of a hypertensive patient caused by spinal anesthesia is not readily explained without recourse to the

17. Steele, J. M., and Kirk, E.: The Significance of the Vessels of the Skin in Essential Hypertension, J. Clin. Investigation **13**:895, 1934.

18. Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System, J. Clin. Investigation **15**:63, 1936.

19. Pickering, G. W.: The Peripheral Resistance in Persistent Arterial Hypertension, Clin. Sc. **2**:209, 1936.

vasomotor system. Possibly during the early stages of essential hypertension heightened vasoconstriction arises from morbid activity of the nervous system but as the disease progresses a local fault of the vessel wall provides for continuance of the disease.

Since alterations of the physiologic state of varied sorts, such as pregnancy, nephritis, pituitary basophilism, constriction of the renal arteries and emotion, often are exhibited by the one sign they have in common, namely, hypertension, the possibility may be entertained that a common substance is liberated which is not directly pressor in action but which acts on the vessel walls to induce hypertonus.

Though the mechanism causing hypertension is not known, it is of importance to ascertain what, if any, influence the nervous system has in its genesis. The operation of Adson and Brown [20] provides such an opportunity.

OPERATION

Section of the anterior roots as we have performed it consists in the bilateral division of the anterior roots of the sixth dorsal to the second lumbar spinal nerve. The positive identification before operation of the spinous process of the first lumbar vertebra and its relation to the overlying skin has been helpful in determining the lower limit of the incision. The identification of the last digitation of the dentate ligament after the dura has been opened has aided in determining the roots to be divided, for it is attached to the dura between the twelfth dorsal and the first lumbar nerve (fig 1).

With the patient under general anesthesia the laminae of the first lumbar to and including the sixth dorsal vertebra are removed in order to expose as widely as possible the dura mater covering the cord. Hemorrhage is meticulously controlled before the dura is opened. The incision in the dura is made in the midline and carried to either extremity of the bony defect. The edges of the incised dura are held apart with a series of fine silk threads, as shown in the accompanying illustration. A rent is made in the pia-arachnoid, and the cerebrospinal fluid is removed by suction.

After the nerves under consideration have been identified the operation of dividing the anterior roots is begun either at the upper or the lower portion of the exposed cord. A fine clamp is placed on the digitation of the dentate ligament close to the dura, and its attachment to the dura is separated with a knife. By drawing the clamp inward or mesially, one can slightly rotate the spinal cord on its long axis, the

20. Adson, A. W., and Brown, G. E.: Malignant Hypertension: Report of Case Treated by Bilateral Section of Anterior Spinal Nerve Roots from the Sixth Thoracic to the Second Lumbar, Inclusive, J. A. M. A. **102**:1115 (April 7) 1934.

maneuver bringing into view the anterior root of the spinal nerve. It is closely applied to the lateral or ventrolateral aspect of the cord and is covered by the pia-arachnoid. It can be readily traced downward and outward to join the posterior root. After the nerve has been identified

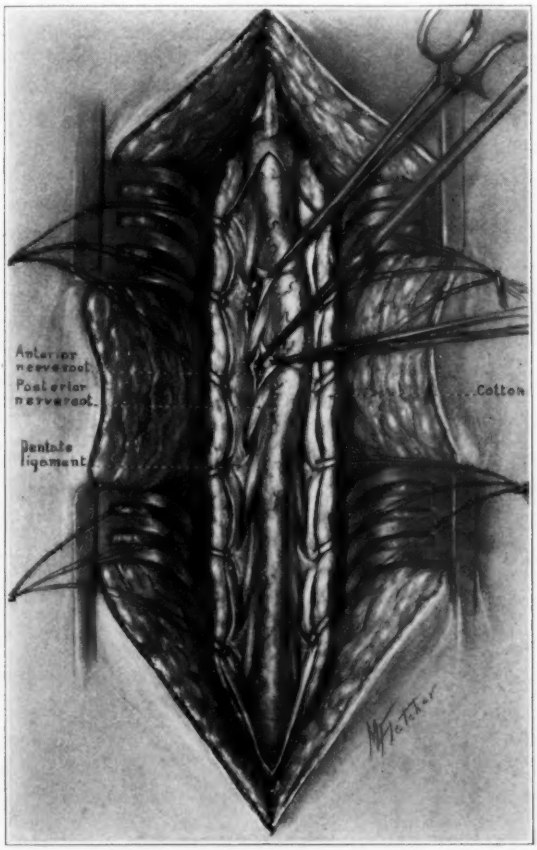

Fig. 1.—Drawing showing the operative field in section of the anterior roots from the sixth dorsal to the second lumbar spinal nerve.

a rent is made in the pia-arachnoid covering it, and the nerve is raised from the cord with a blunt right angle nerve hook. It is doubly ligated with fine silk and divided between the ligatures. The ligature of the nerve is deemed important because of the blood vessels which accompany

it and which in many instances cannot satisfactorily be separated from it. In other cases the accompanying blood vessels are of sufficient size so that they may be separated from the nerve and preserved. Their preservation is desirable, for they contribute to the nourishment of the cord.

In this fashion each pair of anterior spinal nerves is divided, and during the procedure frequent observations of the blood pressure are made by the anesthetist to determine the effect produced. When division of the nerves has been completed, the dura is closed with interrupted fine silk sutures. The muscles, fascia and skin also are closed with interrupted silk sutures.

While from anatomic and physiologic considerations the division of the sixth dorsal to the second lumbar anterior root is probably desirable, we have, as a matter of practice, in only two instances divided all these nerves. In the remaining cases we have omitted division of the sixth dorsal and sometimes of the seventh and eighth dorsal nerves and frequently have omitted division of the second lumbar nerve. Two considerations chiefly have led us to vary the procedure. We have been anxious to determine whether early in cases of essential hypertension the division of the ninth, tenth, eleventh and twelfth dorsal and first lumbar nerves is sufficient to lower the blood pressure significantly, for physiologic experiments indicate that the tenth, eleventh and twelfth dorsal and first lumbar nerves are importantly concerned in controlling the blood pressure. Our observations, still insufficient in number, suggest that in cases of advanced involvement the division of all the nerves mentioned should be undertaken; in patients with an early stage of hypertension division of the ninth dorsal to the first lumbar nerve, inclusive, has thus far sufficed. Again, and especially in early stages, the rapid and sometimes rather alarming fall in blood pressure during the operation has made us hesitate to divide the entire group of nerves. The variation in the reaction of patients on the operating table has led us to divide first the ninth dorsal to the first lumbar nerve, inclusive, and to be guided as regards the division of the others by the patient's reaction. As our experience has increased we have become less fearful of a fall in blood pressure during the operation.

Aside from this fall in blood pressure there is little that occurs during the operative procedure to warrant comment. The preservation of a clear field by the prevention of hemorrhage is the most important point in the performance of section of the roots. In our experience hemorrhage is most likely to occur from the small vessels accompanying the nerve roots and by manipulations too near the point at which the roots perforate the dura. Postoperatively, aside from the low blood pressure,

which we have combated chiefly by intravenous injections of dextrose solution, there have thus far been few serious complications. Difficulty in evacuating the bladder and bowel for forty-eight hours after operation has been fairly frequent and is attributed to the loss of function of the abdominal muscles. In one case the inability to control the bladder persisted for seven weeks after the operation.

In our later experience the operation has been divided into two stages, the first terminating with the completion of the laminectomy and the complete exposure of the dura, the second consisting in the opening of the dura and the division of the anterior nerve roots. An interval of several days to a week was allowed to elapse between stages.

PLAN OF STUDY

Care of the Patient.—Measurements of the blood pressure were made at 9:30 a. m. daily with the patient in bed. During the period of observation before operation, which extended for a month or more, the patient was not allowed out of bed for any purpose. It should be emphasized that *each dot on the graphs under the heading blood pressure usually represents from three to five measurements which were averaged for convenience in charting.* After operation the patient was allowed up at will, but measurements of the blood pressure were made with the patient in bed; hence the measurements cannot be considered strictly comparable with those made before operation. Sedatives, including chloral hydrate, amytal and less often sodium bromide, were employed liberally before but not after operation. The diet was unrestricted as to quality or amount. Electrocardiographic records were made before and after operation by Dr. Alfred Cohn and Miss M. Alleman.

Clinical Observations.—Renal efficiency was measured by the urea clearance test and the ability of the kidneys to concentrate urine. The urea clearance test was employed not only because it is a most delicate test but because Van Slyke, Rhoads, Hiller and Alving [21] have shown that in dogs it parallels the renal blood flow. The specific gravity was measured for a twelve hour specimen voided at the end of twenty-four hours without fluids. If protein was present in sufficient amount to contribute to the specific gravity, a correction was made for it; that is, 0.003 was subtracted from the total specific gravity for each 1 per cent of protein.[22] The number of formed elements in the urine was estimated by the technic of Addis.[23] Not more than 500,000 red blood cells are excreted by a person with normal kidneys. The protein content of the urine was measured by the method of Shevky and Stafford, as slightly modified by MacKay.[24] The protein content

21. Van Slyke, D. D.; Rhoads, C. P.; Hiller, A., and Alving, A.: The Relationship of the Urea Clearance to the Renal Blood Flow, Am. J. Physiol. **110**:387, 1934.

22. Lashmet, F. H., and Newburgh, L. H.: An Improved Concentration Test of Renal Function, J. A. M. A. **99**:1396 (Oct. 22) 1932.

23. Addis, T.: The Number of Formed Elements in the Urinary Sediment of Normal Individuals, J. Clin. Investigation **2**:409, 1926.

24. MacKay, cited by Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 682.

of the plasma was ascertained by the method of Howe,[25] and the hemoglobin content was measured by the Van Slyke and Neill[26] method.

Explanation of the Charts.—On the charts the mean normal of each measurement represented is drawn as a base line; the shaded areas between the base line and the points representing observations indicate the degree of deviation above or below the average normal. The brackets at the left of the scales for urea clearance, concentration of urine and hematuria indicate the range of normal variability. The normal base line for the hemoglobin value varies with the patient's age and sex. As previously stated, measurements of the blood pressure were made daily at 9:30 a. m. *but are represented in the charts as averages.* The black areas representing edema, according to the height of the black area in quarters of the total space, indicate (1) a trace, (2) moderate pitting, (3) marked pitting and (4) general edema with ascites. Morbid changes in the eyegrounds are recorded as follows: (1) constriction of the arterioles, (2) arteriosclerosis, (3) exudate, (4) hemorrhages and (5) papilledema. The estimated time which elapsed between the onset of the disease and the patient's admission to the hospital is recorded on the lowest line of the chart as the first number following the word months. The other numbers in the bottom row indicate months after the patient's first admission to the hospital.

Selection of Patients.—It is possible though not proved that the patient who exhibits marked flexibility in the vascular system will obtain the greatest benefit from section of the anterior roots. The criteria for vascular flexibility which have been employed are of several kinds. The first is a fall in blood pressure when the patient is put to bed. The second is a fall in the blood pressure when colloidal sulfur or acetylbetamethylcholine is injected intramuscularly, when sodium thiocyanate is given by mouth or when amyl nitrite is inhaled. The third is the daily fluctuation in the blood pressure level.

While previous cardiac decompensation and the presence of a markedly enlarged heart, along with changes indicative of myocardial damage as indicated by the electrocardiogram, are not desirable when the operation is elective, it has not been our experience that these interdict it. One case (11), in particular, illustrates this view. Although the heart was greatly enlarged and the T wave was negative in leads I and II, with preponderance of the left ventricle, the patient bore a two stage operation without difficulty.

Extensive changes in the fundi also were considered indicative of a rapidly advancing morbid process, but they did not contraindicate operation. Since the fall in blood pressure has not appeared to reduce the renal efficiency, as measured by the urea clearance test or the ability to concentrate urine, moderate degrees of renal insufficiency (above 30 per cent of the normal urea clearance) may not jeopardize the life of the patient.

We have not considered it justifiable to select only those patients in whom, in our opinion, a maximum fall in blood pressure might occur. Some have been operated on in the terminal stage of the disease and some who have shown little evidence of vascular flexibility have been operated on in the hope that the blood pressure might be reduced, contrary to our prognosis.

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25. Howe, P. E.: The Determination of Proteins in the Blood—a Micro Method, J. Biol. Chem. **49**:109, 1921.

26. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:573, 1924.

REPORT OF CASES

CASE 1.—The history of this patient has been reported previously.[27] We wish to add to this record that it is now thirty-seven months since the operation was

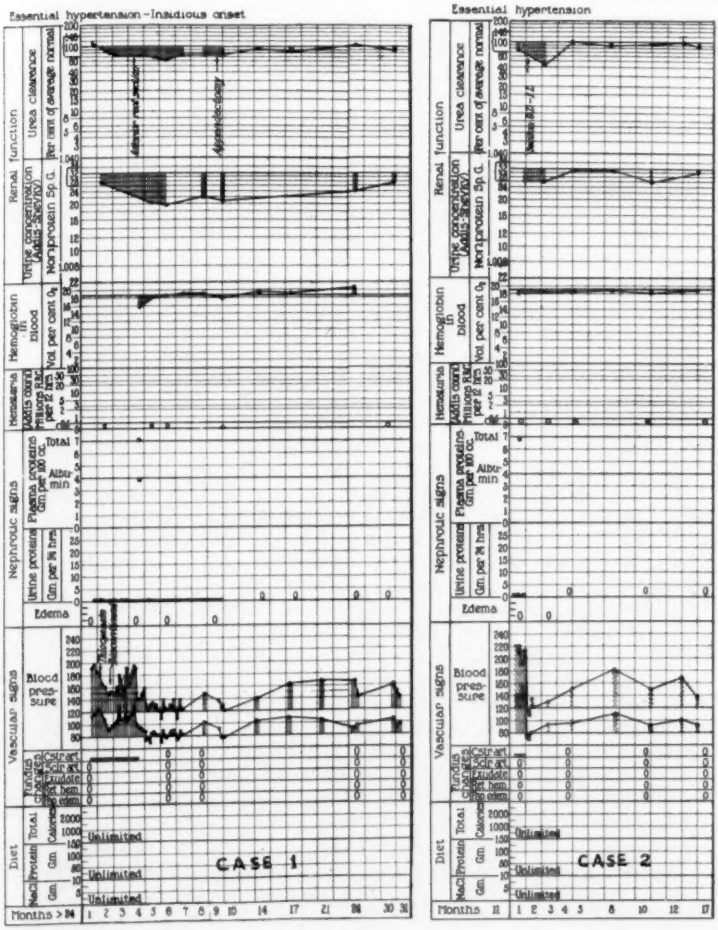

Fig. 2.—Case 1 was that of a woman aged 23 with essential hypertension of insidious onset. She was 157 cm. tall, and her ideal weight was 57 Kg. Case 2 was that of a woman aged 24 with essential hypertension. She was 165.5 cm. tall, and her ideal weight was 61.5 Kg.

27. Page, I. H., and Heuer, G. J.: A Surgical Treatment of Essential Hypertension, J. Clin. Investigation **14**:22, 1935.

performed. The symptoms have not returned, and the patient has resumed her work in an office. The blood pressure level after one-half hour's rest in bed varies from 140 systolic and 106 diastolic to 162 systolic and 110 diastolic. The renal function has remained normal, and there has been no change in the size of the cardiac shadow, as measured on an x-ray plate. Since considerably more data on this patient are now available, the graphic chart is again presented. Dr. E. V. Allen concurred with us as to the advisability of operation in this case.

CASE 2.—A 24 year old housewife, referred to us by Dr. M. C. Rosenkranz, complained of dizziness, nausea, weakness, nervousness and ringing in the ears. Her father died of hypertension at 44 years of age. One sister 32 years old has had hypertension for five years. Four years ago this patient noticed that she had attacks during which her face and the upper part of the chest became spontaneously blotchy red; she had spots before her eyes and some dizziness. The arterial pressure was found to be 130 mm. For the past year she had been distressed by nervousness, emotional instability, ringing in the ears, nausea, insomnia, weakness and dizziness. Eight months previous to her admission to the hospital the arterial pressure was 180 mm., and four months later it was 220 mm. Recently there was a slight loss of memory.

The patient was of masculine build, and there was a somewhat masculine distribution of hair. The beard was almost masculine. The disks of the fundi were sharply outlined and slightly hyperemic. There was slight sausage-shaped constriction in some of the arterioles, and the veins were moderately dilated. There was no perivasculitis, hemorrhage or exudate. The thyroid gland was slightly and diffusely enlarged, but there were none of the classic signs of exophthalmic goiter. The size of the heart was normal, as measured by percussion, and it was not overactive. The aortic second sound was clearly accentuated. Measurements from an x-ray plate showed a total transverse diameter of 10.5 cm. and an internal diameter of the chest of 22 cm. The peripheral vessels were a little thickened but not tortuous. The coloring of the skin of the extremities was unusual, being mottled deep pink and bluish. Both the hands and the feet were cold and covered with perspiration. Both superficial and deep reflexes were equal on the two sides and moderately active.

The basal metabolic rate was + 15 per cent. The electrocardiographic record showed that the T wave was positive in leads I and II and negative in lead III. The conduction time was 0.15 second. There was preponderance of the left ventricle, and the rhythm was normal. Roentgenograms of the skull showed it to be normal. The Kline test was negative.

The blood pressure when the patient had been at rest in bed for nineteen days varied from 180 systolic and 130 diastolic to 220 systolic and 160 diastolic, the average level being 206 systolic and 148 diastolic.

Section of the anterior roots from the ninth thoracic to the first lumbar segment on the left side and from the ninth to the twelfth thoracic segment on the right side was performed on Nov. 2, 1934. During the operation the arterial pressure fell from 195 systolic and 140 diastolic to 120 systolic and 70 diastolic.

The postoperative course was uneventful. The blood pressure averaged from 130 to 148 systolic and from 90 to 96 diastolic for the first four months. The improvement in the subjective symptoms was remarkable. The patient has returned to work.

Comment.—This patient had hypertension which appeared to be rapidly advancing. The disease was found in other members of her family. Four years prior to her admission to the hospital the arterial

pressure was normal, but eight months before her admission to the hospital it was 180 mm. and four months later 220 mm. She suffered from many subjective symptoms. The "hypertensive diencephalic syndrome" was especially marked. Rest in bed and sedatives did not reduce the pressure significantly. Five anterior roots were severed on one side and four on the other (ninth thoracic to first lumbar segment). The arterial pressure fell from an average level of 206 systolic and 148 diastolic to 140 systolic and 94 diastolic and remained there for about five months. Since then (in fifteen months) it has risen to 170 systolic and 110 diastolic. The subjective symptoms, excepting those included in the "diencephalic syndrome," disappeared, and the patient now works from 9 in the morning to 6 at night in a store.

CASE 3.—A 17 year old girl had complained of headaches and dizziness for three years. There was no history of vascular disease in the family. For the past few years she had noticed that she blushed extremely easily and simultaneously had palpitations, sweating and slight shortness of breath. She had had dull pains over the precordium.

One year before her admission to the hospital she decided to withdraw from the world and become a nun. The arterial pressure was found to be 150 systolic and 102 diastolic. Her emotional make-up was highly unstable, and she suffered from many conflicts. She was referred to Dr. S. Clinton Levine, who found that the pressure was 174 systolic and 124 diastolic. Six months later she was admitted to the hospital.

Physical examination showed that the girl was well proportioned. She did not appear ill. She blushed violently, the blush extending down over the upper part of the chest, and over the same area were small beads of perspiration. The hands and feet were cold. The distribution of hair was normal. The nerve heads of the eyegrounds were slightly hyperemic, but no papilledema was present. The arterioles were tortuous (grade 2), but there was almost no perivasculitis. The veins were slightly dilated. There was no hemorrhage or exudate. The thyroid gland was slightly and diffusely enlarged. The heart was overactive, and the rate was 88. It was not enlarged. Measurements made from an x-ray plate showed a total transverse diameter of 10.2 cm., and the internal diameter of the chest was 23.5 cm. The heart was pear shaped and the aorta normal. The aortic and pulmonic second sounds were not accentuated. The peripheral vessels were not thickened. Both superficial and deep reflexes were active and equal on the two sides. None of the classic symptoms of exophthalmic goiter were present except slight enlargement of the gland.

The electrocardiogram showed a positive T wave in leads I and II and a negative T wave in lead III, a PR interval of 0.16 second, preponderance of the left ventricle and normal rhythm. The basal metabolism varied from —11 to +8 on a number of occasions. The blood sugar value was 103 mg. per hundred cubic centimeters. The sella turcica was small, but the floor was clearly defined. The Kline and Wassermann tests were negative. The blood pressure during the preliminary examinations in the outpatient clinic varied from 190 systolic and 136 diastolic to 210 systolic and 144 diastolic. When the patient was admitted to the hospital it quickly fell to an average of 180 systolic and 122 diastolic, falling as low as 136 systolic and 94 diastolic at one reading. After the patient

had been in the hospital for five weeks the pressure was still elevated, the diastolic pressure, in particular, reaching 130 mm. or more.

On Dec. 18, 1934, the anterior nerve roots from the ninth thoracic to the first lumbar segment, inclusive, were severed. The postoperative course was

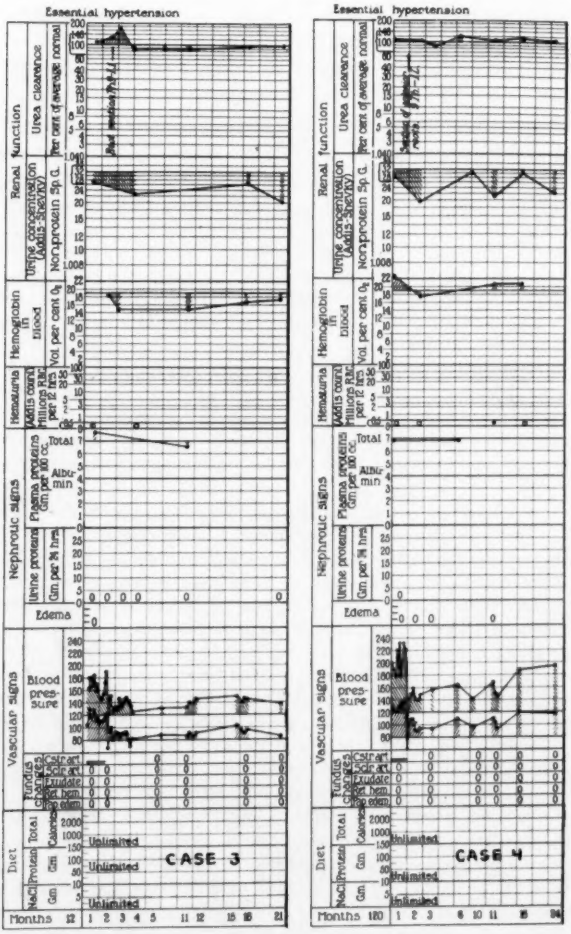

Fig. 3.—Case 3 was that of a girl aged 17 years with essential hypertension. She was 160.5 cm. tall, and her ideal weight was 58.3 Kg. Case 4 was that of a woman aged 32 with essential hypertension. She was 158.5 cm. tall, and her ideal weight was 50.8 Kg.

uneventful. Distention was easily controlled by pitressin and enemas. The patient was allowed up on the fourteenth postoperative day. The arterial pressure

fell to 100 systolic and 70 diastolic on the day of operation. During the next weeks it averaged 130 systolic and 84 diastolic. Reduced iron was administered to aid in overcoming a slight degree of anemia which had developed. There was little change in the fundi of the eyes. Twenty-six months after operation the patient appeared to be in good health. Excitement caused the arterial pressure to rise to 162 systolic and 106 diastolic, but the level after rest was 138 systolic and 90 diastolic. The attacks suggestive of the "diencephalic syndrome" were somewhat less severe than before operation. All other symptoms had disappeared.

Comment.—This was a case of marked hypertension in a young girl. Symptoms and signs of the "hypertensive diencephalic syndrome" were prominent. Five pairs of anterior nerve roots were sectioned (ninth thoracic to first lumbar). The blood pressure fell from an average preoperative level of 180 systolic and 122 diastolic to 138 systolic and 90 diastolic and has remained at this level for twenty-six months. Except for the "diencephalic syndrome," all subjective symptoms disappeared. The operation was considered successful.

CASE 4.—A 32 year old woman, referred to us by Dr. H. Meyersburg, had noticed shortness of breath which was unrelated to physical exertion twelve years before her admission to the hospital. At that time she was emotionally upset, and one year later suffered a "nervous breakdown." She was married the following year. Two years later a dead fetus was delivered. The physician told her that she had hypertension and excreted a small amount of albumin. Her emotional instability increased, and two years later she was divorced. Since then emotional instability and a feeling of pressure in the head and abdomen have been the outstanding symptoms. For the past ten years she had been greatly embarrassed by spontaneous blushing, which caused the skin of her face and the upper part of the chest to become mottled red and white. Her mother and sister also exhibited this phenomenon, and the sister, in addition, suffered from hypertension.

The patient was a well developed woman, obviously high strung and nervous. The distribution of hair was normal. Examination of the fundi showed that the nerve heads, arterioles and veins were normal. No perivasculitis, exudate or hemorrhages were noted. The heart was not enlarged, as measured by percussion. X-ray measurements showed a total transverse diameter of 10.6 cm. and an internal diameter of the chest of 23.6 cm. The rate, rhythm and sounds were normal. The peripheral vessels were not thickened or tortuous.

The electrocardiogram showed an upright T wave in leads I and II and a negative T wave in lead III, sinus tachycardia, a conduction time of 0.16 second and a normal rhythm. The basal metabolic rate was (first test) —12 per cent and (second test) —7 per cent. Three days later it was (first test) + 32 per cent and (second test) + 11 per cent. The Wassermann test was negative. The arterial pressure varied from 176 systolic and 126 diastolic to 230 systolic and 145 diastolic during the first twenty days the patient was in bed. The average pressure was 210 systolic and 130 diastolic. While the blood pressure was relatively fixed at an elevated level, particularly the diastolic pressure, the cardiac and renal functions were good.

On Nov. 30, 1934, the anterior roots from the ninth thoracic to the first lumbar segment were cut. During the operation the arterial pressure fell from 190 systolic and 130 diastolic to 110 systolic and 70 diastolic. The postoperative

course was uneventful, and fourteen days later the patient was allowed to walk. The blood pressure fell to an average level of 160 systolic and 104 diastolic, but after twenty-two months it was 190 systolic and 118 diastolic. The "diencephalic syndrome" continued unaltered, but the sensation of pressure in the head and abdomen disappeared. The abdomen protruded slightly but not sufficiently to require a binder. The superficial abdominal reflexes were absent, and there was no change in cutaneous sensibility. Emotional excitement caused the arterial pressure to rise to 200 systolic and 130 diastolic. Measurements of the heart from x-ray plates taken eleven months after the operation showed no change from the preoperative size.

Comment.—Section of five pairs of anterior roots (ninth thoracic to first lumbar) clearly reduced the blood pressure in this case. Associated with the reduction in arterial pressure was the disappearance of the sensation of pressure in the head and abdomen but no change in the intensity or the frequency of the attacks characterized as the "hypertensive diencephalic syndrome." After eleven months it appeared that emotional instability was still present. Twenty-seven months after operation the arterial pressure had risen to a level somewhat below the preoperative level. The patient felt much improved but the blood pressure had not been permanently reduced.

CASE 5.—A 25 year old housewife, referred to us by Dr. Mary Halton, complained chiefly of daily headaches for the past year and one-half. Hypertension had not occurred in her family. She said she thought she was more than normally excitable. Six years before her admission to the hospital the blood pressure was found to be 95 systolic and 60 diastolic. Three years before her admission to the hospital the arterial pressure was again measured because of insomnia and nervousness and was found to be 142 systolic and 90 diastolic; one year before admission it was 150 systolic and 95 diastolic; five months before admission it was 170 systolic and 100 diastolic, and on admission it was 182 systolic and 116 diastolic. Loss of appetite, restlessness, fatigability, dizziness, faintness and severe headaches were the outstanding symptoms. She also had attacks characterized by flushing of the face, involuntary crying and palpitation. Shortness of breath on exertion was noticed a few months before admission. She noticed that the hair on her body has grown rapidly in the past two years. Nocturia occurred (six or eight times a night).

The patient was a well developed woman. The coarse, abundant hair showed a masculine type of distribution. She appeared nervous and perspired freely. The disks of the fundi were normal, and the arterioles in some places showed slight tortuosity and sausage-like constriction. There was almost no perivasculitis. Hemorrhages or exudates were not seen. The tonsils had been removed. The thyroid gland was not palpable. The heart was of normal size, as measured by percussion. Roentgenograms showed a maximum diameter of 7.5 cm. on the left and 4.5 cm. on the right, a total transverse diameter of 12 cm. and an internal diameter of the chest of 25 cm. The sounds were of good quality, and the aortic and pulmonic second sounds were not accentuated. The pulse rate was 104. The peripheral vessels were not thickened. There was no tremor in the outstretched fingers. Both superficial and deep reflexes were equal in strength on the two sides but hyperactive. The electrocardiographic record showed

T waves positive in all leads, a conduction time of 0.14 second, a diphasic P wave in lead III and preponderance of the left ventricle. The sella turcica appeared normal in an x-ray plate.

During the first twenty-seven days that the patient was in bed without treatment other than sedatives, the arterial pressure varied from 148 to 264 systolic

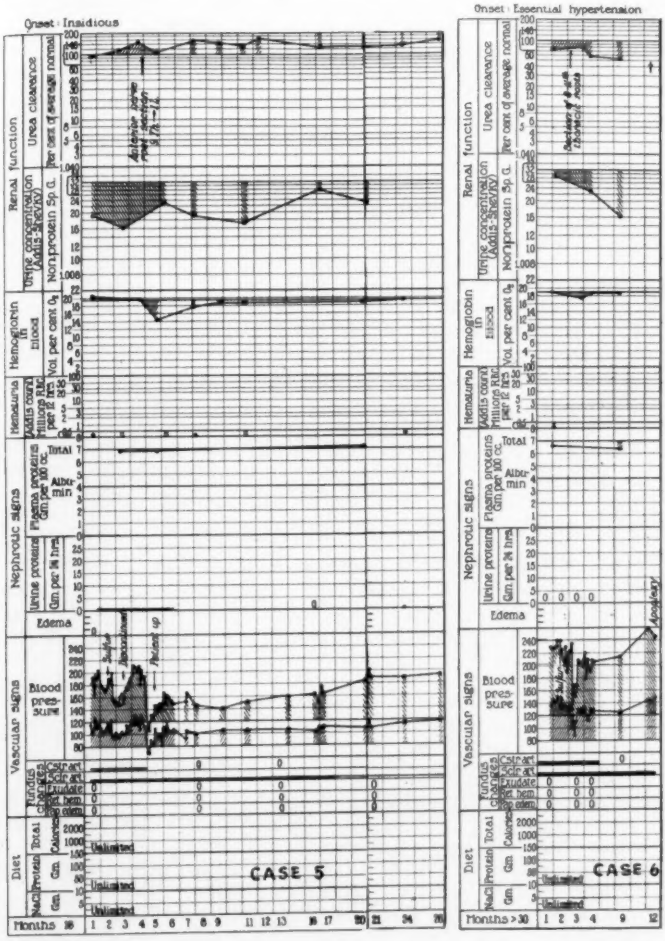

Fig. 4.—Case 5 was that of a woman aged 25 with essential hypertension of insidious onset. She was 150.5 cm. tall, and her ideal weight was 50.6 Kg. Case 6 was that of a woman aged 40 with essential hypertension. She was 167 cm. tall, and her ideal weight was 62.8 Kg.

and from 90 to 148 diastolic, averaging about 184 systolic and 116 diastolic. Colloidal sulfur, 1 cc. twice daily, reduced the arterial pressure to an average level of 152 systolic and 100 diastolic, but even under this treatment it slowly rose to 170 systolic and 100 diastolic. When this treatment was discontinued it rose to 210 systolic and 116 diastolic. After fourteen weeks of rest in bed the pressure had risen from 182 systolic and 116 diastolic to 200 systolic and 122 diastolic. The patient complained regularly of severe headaches, fleeting pains throughout the body and tightness over the scalp.

On Oct. 29, 1934, laminectomy was performed from the sixth thoracic to the second lumbar segment. Because the blood pressure varied precariously, the operation was done in two stages. Two days later the wound was reopened and the anterior nerve roots were severed from the sixth thoracic to the second lumbar segment, inclusive. The course was uneventful except for considerable distention. An intravenous pyelogram showed that no pathologic changes had occurred in the renal pelves. During convalescence the arterial pressure varied considerably and after four weeks averaged 146 systolic and 106 diastolic. Four months after operation it was 140 systolic and 100 diastolic and seven months later 152 systolic and 106 diastolic. The subjective symptoms disappeared completely. Constriction in the arterioles of the retina was no longer observed.

Comment.—This was a case of severe hypertension in a young woman of more than a year's duration with marked subjective symptoms. Anatomic changes in the vascular system were not evident. Nine pairs of anterior roots were severed (sixth thoracic to second lumbar). An average fall in pressure of 38 mm. systolic and 10 mm. diastolic occurred, and the wide swings in pressure (up to 264 systolic and 148 diastolic) disappeared. The subjective symptoms were no longer present, except for occasional headaches.

Case 6.—A 40 year old woman, referred to us by Dr. Walter Niles, complained of headaches and a change of disposition for sixteen months. She led a busy life as a supervisor of stenographers. Sixteen months before admission to the hospital she noticed that she was becoming exceedingly nervous and irritable and that she tired easily. A dull continuous pain was felt over the precordium, and exertion caused palpitations and dyspnea. Eight months before her admission to the hospital swelling of the ankles occurred in the evening. Pressure and a feeling of constriction over the vertex became annoying symptoms along with repeated severe headaches. The menstrual periods were regular, and the flow was more profuse than usual. There was a marked decrease in libido. Three months before her admission the left arm became numb, white and cold up to the elbow. This attack lasted for about ten days and disappeared without residual paralysis. The blood pressure was 210 mm. systolic one year before admission and 230 mm. systolic three months before admission. In the past month headaches and fatigue had been so severe as to confine the patient to her room.

Examination disclosed that the patient was a well developed, slightly overweight woman. The disks of the fundi were normal, but the arterioles were constricted (grade 2) and tortuous (grade 2), especially in the macular field. There was practically no perivasculitis. The veins were dilated (grade 3) and tortuous, and arteriovenous compression was observed. There was no hemorrhage or exudate. The thyroid gland was not palpable. The heart beat had a moderate thrust and was increased in rate above normal. The measurements from an x-ray plate

showed a total transverse diameter of 14.8 cm. and an internal diameter of the chest of 26 cm. The aorta was tortuous and more radio-opaque than normal. The sounds were of good quality, but the aortic second sound was markedly accentuated and the pulmonic second sound less so. The peripheral vessels were slightly thickened. The abdominal wall was relaxed and flabby. Roentgen examination of the skull showed that the sella turcica was normal.

The electrocardiogram showed positive T waves in leads I and II and a negative T wave in lead III, a conduction time of 0.16 second, preponderance of the left ventricle and a normal rhythm. The Wassermann reaction was negative. The basal metabolic rate was + 1. The arterial blood pressure varied from 208 to 260 mm. systolic and from 132 to 160 mm. diastolic, averaging 230 systolic and 142 diastolic during fourteen days of rest in bed. Intramuscular injections of colloidal sulfur reduced the pressure to a minimum of 180 systolic and 122 diastolic within fifteen days.

On March 7, 1935, laminectomy was performed, and the anterior roots were severed from the ninth to and including the twelfth. Marked calcific arachnoiditis was found, which increased the difficulties of the operation greatly. The postoperative course was uneventful. The arterial pressure varied from 180 to 220 mm. systolic and from 110 to 138 mm. diastolic, averaging 210 systolic and 122 diastolic, with the patient up and about the ward during the next month and a half. The electrocardiogram was unchanged. After the operation the subjective symptoms disappeared. The absence of headaches was striking. The patient died of apoplexy nine months after operation.

Comment.—This patient suffered from marked generalized arteriosclerosis as well as hypertension. The arterial pressure was fixed at a high level and showed little flexibility. Dr. Niles agreed with us that because of the severe subjective symptoms and the hopeless outlook operation should be attempted. Because of the difficulty of operating on a spinal cord covered with arachnoidal calcified plaques, only four pairs of dorsal roots were cut. The fall in arterial pressure averaged 20 mm. systolic and 20 mm. diastolic and was associated with a disappearance of the subjectvie symptoms. Death occurred from apoplexy nine months after operation.

Case 7.—A 35 year old housewife complained of headaches, precordial pain, dizzy spells, easy fatigability and dyspnea on exertion for three years. There was no history of vascular disease in the family. Three years before her admission to the hospital hypertension was discovered by her physician, Dr. J. Auslander. Since then, severe headaches lasting for days has been the most characteristic symptom. There has been no change in the menses or libido.

Examination showed that the patient was well developed and did not appear ill. Corneal opacities were present in both eyes, and the pupils reacted to light and in accommodation actively. The arterioles of the fundi were slightly constricted and tortuous, and the disks were normal. There was no hemorrhage or exudate. The thyroid gland was moderately and diffusely enlarged without bruit. No other signs of exophthalmic goiter were found. The heart was not enlarged. Measurements from an x-ray plate showed a maximum diameter of 8.9 cm. to the left and 2.9 cm. to the right, a total transverse diameter of 11.8 cm. and an internal diameter of the chest of 25 cm. The aorta was dilated and prominent. The

aortic second sound was accentuated. The cardiac rate was 96. The deep reflexes were hyperactive. Marked generalized vascular sclerosis was present. A roentgenogram of the skull showed that the sella turcica was normal. The Wassermann reaction was negative. The electrocardiogram showed a positive T wave in all three leads, a PR interval of 0.18 second, a deep Q_3 wave in lead III and

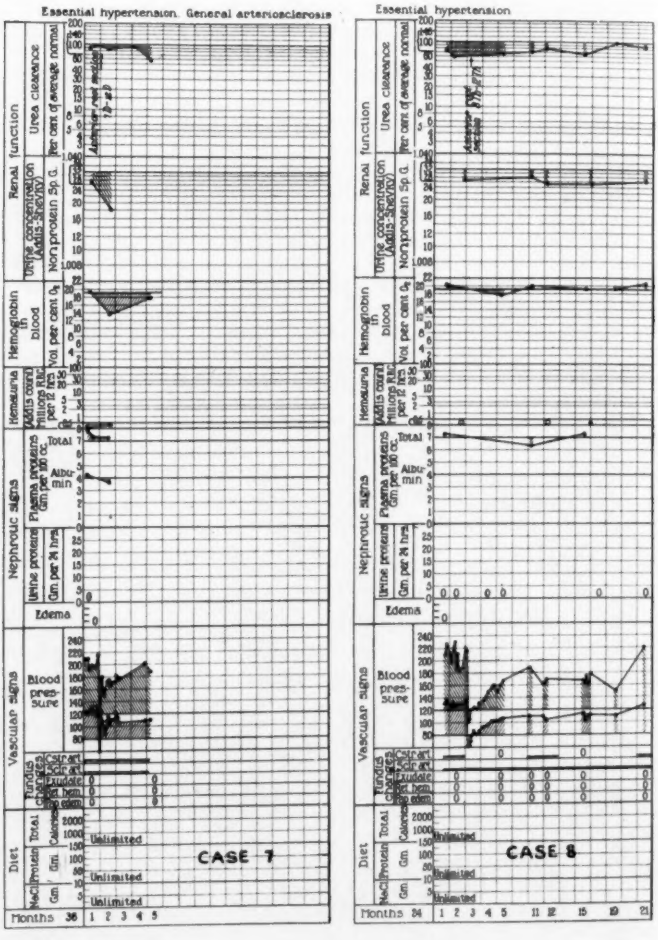

Fig. 5.—Case 7 was that of a woman aged 35 with essential hypertension and generalized arteriosclerosis. She was 156.5 cm. tall, and her ideal weight was 56.8 Kg. Case 8 was that of a woman aged 25 with essential hypertension. She was 150.7 cm. tall, and her ideal weight was 50.3 Kg.

a normal rhythm. The basal metabolic rate was + 7 per cent. When the patient was admitted to the hospital the arterial pressure was 212 systolic and 126 diastolic and varied from 182 to 212 mm. systolic and 108 to 132 mm. diastolic during fourteen days of rest in bed. The average pressure was 190 systolic and 122 diastolic.

On Jan. 25, 1935, the anterior nerve roots from the seventh to the twelfth thoracic segment were severed. The arterial pressure fell to 90 systolic and 60 diastolic immediately after the operation. There was difficulty in voiding after the operation, and frequent catheterization was necessary. The patient sat up on the ninth day. Gastric analysis was performed before and seventeen days after operation. No marked difference was found in either free or total acid in the specimen taken during fasting or that obtained after the injection of 0.5 mg. of histamine.

The arterial pressure varied from 160 to 184 mm. systolic and from 98 to 122 mm. diastolic during thirty-nine days of convalescence. The average was 176 systolic and 114 diastolic. This level was not strictly comparable with the preoperative level, bacause it was measured with the patient up and about the ward instead of in bed. Four months after operation the arterial pressure at a single examination was 200 systolic and 120 diastolic. There was no apparent postoperative change in the size of the cardiac shadow, and there were no changes in the eyegrounds.

Comment.—This was a case of essential hypertension of long duration but relatively benign. Subjective symptoms were marked before operation. Six pairs of anterior roots (seventh to twelfth thoracic) were cut. While almost complete symptomatic relief was obtained, the arterial pressure during the first four months fell on an average of only 14 mm. systolic and 10 mm. diastolic. It is our present opinion that the course of the disease was not significantly altered.

Case 8.—A 25 year old nurse, referred to us by Dr. C. Boettiger, of Flushing, Long Island, complained of headaches, nausea and dizziness for two years. She stated that she had rheumatic fever with swollen joints at the age of 7 years. Seven years before admission to the hospital she had an appendectomy performed, after which pneumonia developed. Two years before her admission to the hospital a physician told her that she had rheumatic heart disease. She had always been nervous and high strung. For the past few years she noticed that she perspired freely and that her hands and feet were usually cold and moist. Flushing of the skin of the face and the upper part of the chest, palpitations, crying without apparent reason and consciousness of increased intestinal movements became annoying symptoms. Two years before admission a life insurance policy was granted, although her blood pressure was 140 mm. systolic. In the past year excruciating headaches which often lasted for two days occurred, usually associated with nausea, dizziness and a feeling of constriction of the scalp. After a day's work she often had marked edema of the ankles, which disappeared after rest. She smoked heavily. The arterial pressure had risen to over 200 mm. within the past two years.

The patient was a well developed, highly nervous and irritable woman, appearing greatly depressed. The distribution of hair was normal. There was acne vulgaris over the skin of the face and chest. Examination of the fundi showed that the nerve heads were hyperemic but sharply outlined and without papilledema.

The arterioles were straightened and constricted (grade 2). An early stage of perivasculitis was present. The veins were dilated, and arteriovenous compression was observed. There was no hemorrhage or exudate. The thyroid gland was not enlarged. The heart was overactive and the rate 96. It was not enlarged. Roentgen measurements showed a total transverse diameter of 12.6 cm. and an internal diameter of the chest of 23 cm. The first sound was snapping in character and was followed by a short systolic whiff. Both the aortic and the pulmonic second sound were markedly accentuated. The peripheral vessels were slightly thickened. Both the superficial and the deep reflexes were active but more so on the left than on the right. Roentgenograms of the skull disclosed that the vessels within the bone of the vault were markedly calcified. The sella turcica was normal. The pineal gland was calcified. There was no calcification of the peripheral vessels. The electrogardiograph record showed a positive T wave in leads I and II and a negative T wave in lead III, a PR interval of 0.16 second, preponderance of the left ventricle and a normal rhythm. After eight days of rest in bed the blood pressure varied from 240 to 170 mm. systolic and from 138 to 112 mm. diastolic, averaging 210 systolic and 130 diastolic. Intramuscular injections of colloidal sulfur and oral administration of sodium thiocyanate reduced the pressure slightly. The patient felt badly during most of her stay in the hospital, prostrating headaches alternating with severe mental depression. The level of the arterial pressure varied widely and showed little tendency to fall.

On Jan. 7, 1935, the anterior nerve roots were severed from the eighth thoracic to the first lumbar segment, inclusive. The blood pressure fell to 90 systolic and 40 diastolic immediately after the operation and gradually rose to an average level of 148 systolic and 94 diastolic. Fecal and urinary incontinence developed but slowly disappeared. Bowel movements were obtained for a few weeks after the operation only by the use of enemas and injections of solution of posterior pituitary. It was found that the ethyl ester of betamethylcholine chloride often produced effective bowel movements.

The vital capacity before operation was 2,100 cc. and after operation 1,500 cc. The waist measurement was 69.5 cm. before operation and 75 cm. after operation. Fluoroscopy of the diaphragm showed movement of 3 or 4 cm. on both sides, which was unchanged after section of the roots. Tests showed that sweating was absent over an area of the skin of the abdomen extending from slightly below the costal margin to the pubis. Gastric analysis showed the presence of free hydrochloric acid and a total acidity of 105. After operation the total acidity was 108. Reexamination of the eyegrounds showed that the right disk was still slightly hyperemic and the arterioles were no longer constricted. No arteriovenous compression was present. The size of the veins was normal, the change being marked in comparison with the preoperative status. The aortic and pulmonic second sounds were still accentuated. The mental depression continued for several months in spite of the fact that the blood pressure was not far above normal, but it was less marked. She still exhibited the attacks of blushing, lacrimation and palpitation, during which the arterial pressure rose to 180 systolic and 124 diastolic, but they were not as intense as before the operation. She was uncooperative and continually had difficulty with other patients and nurses. Indeed, it was difficult to measure the blood pressure when she was not angry at something. It varied from 140 to 190 mm. systolic and from 90 to 110 mm. diastolic. The average pressure was 164 systolic and 110 diastolic nine months after operation but rose to 220 systolic and 122 diastolic, nine months later. After operation she had headaches rarely, and these were not severe. Nine months after operation her whole attitude seemed to change, and she is now an agreeable person.

Comment.—This was a case of severe hypertension in a girl with neurotic tendencies. Emotional instability and racking headaches were the outstanding symptoms. Six pairs of anterior nerve roots (eighth thoracic to first lumbar) were severed. The fall in blood pressure averaged 60 mm. systolic and 25 mm. diastolic. After nineteen months it slowly rose to a level a little below that observed before operation. The headaches largely disappeared, and she was able to resume her work as a nurse. The mental depression from which she suffered has almost disappeared, and on the whole she feels much improved.

CASE 9.—A 26 year old housewife complained of blurring of the vision for one year. There was no vascular disease known in the family. She had had scarlet fever at the age of 14 years. Eight years before admission to the hospital she had consulted a physician because of burning and itching on urination, and sugar was found in the urine. It was possible to control the diabetes by means of diet. One year before admission to the hospital she missed a menstrual period. Two months later the arterial pressure was found to be 168 mm. systolic. Protein was found in the urine. At that time she complained of dimness of vision, and a month later a hemorrhage was observed in the right fundus. A few weeks later another one occurred in the left fundus. Vision became steadily diminished until at the time of admission she was unable to distinguish objects held close to her eyes. At times swelling of the ankles occurred. Four months after she became pregnant an abortion was performed. Shortly before this an infection of the toe occurred, with cellulitis which spread up the leg, resulting in an abscess in the calf muscles. She noticed that after the abortion she became nervous, lacked ambition, tired easily and was unable to sleep normally. The menstrual periods became irregular, and she lacked libido. Nocturia also occurred. Eleven months after the onset of symptoms she entered the Presbyterian Hospital. Dr. F. D. Mott and Dr. Wilcox kindly furnished us with the following information. The blood pressure was 168 systolic and 90 diastolic. Partial detachment of the retina was observed, with marked exudation. Preretinal and vitreous hemorrhages also were noted. The blood sugar content was 170 mg. per hundred cubic centimeters, and the creatinine content was 1.6 mg. The Wassermann reaction of the blood was negative. The basal metabolic rate was —6 per cent. During her stay of one month in the hospital the urea content rose from 55 to 84 mg. per hundred cubic centimeters of blood. The patient's weight fell from 165 to 147 pounds (75 to 67 Kg.).

Physical examination showed that the patient was short, overweight and almost blind. The distribution of hair was normal. The skin of the trunk was abnormally brown. The pupils reacted sluggishly to light. The patient could count fingers at 6 inches (15 cm.). In the right eye was a large opacity in the vitreous and a deeper hemorrhage into the vitreous. There was extensive hemorrhage in the neuro-epithelial layers of the retina. Detachment of the retina had occurred in both fundi, and hemorrhages were present. The remnants of the vessels were tortuous and of uneven caliber. A purulent, necrotizing lesion of the gum margin was present, with erosion of the base of the teeth. The heart rate was 96. Measurements made on percussion showed it to be markedly enlarged to the left and to the right. The sounds were of good quality. The aortic and pulmonic second sounds were slightly accentuated. The arterial pressure was 198 systolic and 98 diastolic. The edge of the liver was palpated 2 cm. below the costal margin.

The electrocardiogram showed a negative T wave in lead I and an upright T wave in leads II and III, notching of R_1 and preponderance of the left ventricle. The urea clearance on admission was 18 per cent of normal, but within fourteen days

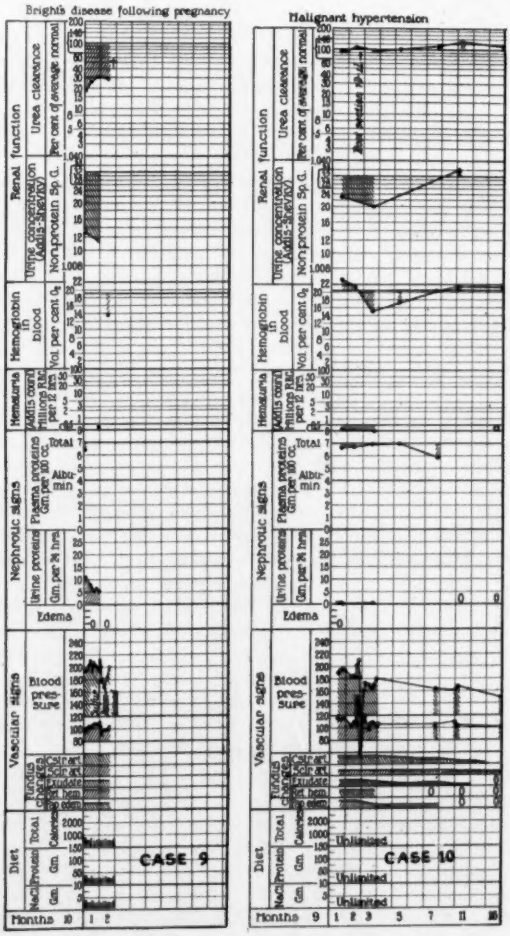

Fig. 6.—Case 9 was that of a woman aged 26 with Bright's disease and hypertension following pregnancy. She was 162 cm. tall, and her ideal weight was 59.5 Kg. Case 10 was that of a man aged 24 with malignant hypertension. He was 176.5 cm. tall and his ideal weight was 69 Kg.

it had risen to 26 per cent of normal. The blood pressure varied from 170 to 212 mm. systolic and from 90 to 114 mm. diastolic, averaging 200 systolic and 110 diastolic for a period of seven weeks in bed.

Comment.—It was realized that this was a case of hopeless malignant arteriolar nephrosclerosis with neuroretinopathy, detachment of the retinas, cardiac hypertrophy and hypertension. It was not known whether reduction of the blood pressure would be of any value. As a last resort the patient was subjected to section of the anterior roots on June 20, 1934. During the latter part of the operation the blood pressure varied alarmingly. The roots from the sixth to the twelfth thoracic segment were severed. While the dura was being closed the patient stopped breathing. Dr. R. Parsons performed an autopsy. No hemorrhage was found in the cord. The primary diagnosis was generalized arteriolar sclerosis, arteriolar nephrosclerosis, arteriosclerosis with calcification of the aorta and its branches, detachment of the retinas with hemorrhage into them and partial atelectasis of the lungs. Accessory anatomic diagnoses were a persistent thymus gland, cholelithiasis and follicular cysts of the ovaries.

Case 10.—A 24 year old insurance clerk, referred to us by Dr. J. E. Hutchinson and Dr. T. H. Denne, of Hartford, Conn., complained of blurring of vision in both eyes and severe headaches for four and a half months before entry into the hospital. There was no familial history of hypertension. He was excitable and nervous. Eight months previously a stone had been removed from the pelvis of the right kidney. The blood pressure was normal at that time. Five weeks later he began to have dull headaches which appeared early in the morning and lasted until noon. These became progressively more severe. Three and one-half months later the vision in the right eye began to fail. Marked papilledema with hemorrhages and exudate was noted in the fundus of the right eye, and less marked changes were present in the left eye. Vision in the left eye was 20/20 and in the right eye 20/70. The basal metabolic rate was —4 per cent. The Wassermann reaction of the cerebrospinal fluid and blood was negative. The arterial blood pressure was 210 systolic and 140 diastolic. During the next four months the vision improved slightly, but the headaches continued. The patient had had no cardiac symptoms or signs.

Physical examination showed that the patient was a well developed man, who did not appear ill. There was bilateral papilledema (3 or 4 diopters). The disks were surrounded by large "cotton wool" exudates, and two hemorrhages were seen in the nasal portion of the left retina. The arterioles were irregular and constricted. The thyroid gland was not palpable. The heart was not enlarged. Measurements of the cardiac shadow on an x-ray plate showed a total transverse diameter of 13.1 cm. The internal diameter of the chest was 26 cm. The pulse rate was 86. The heart sounds were of good quality. The peripheral vessels were slightly thickened. The reflexes were hyperactive and equal on the two sides. An electrocardiogram showed a PR interval of 0.17 second, a positive T wave in leads I and II and a negative T wave in lead III and high voltage of the QRS complex in all leads. The sella turcica was normal in appearance on an x-ray plate. The blood sugar value was 86 mg. per hundred cubic centimeters. During twelve days of rest in bed the blood pressure varied from 182 to 232 mm. systolic and from 112 to 132 mm. diastolic, averaging 190 systolic and 120 diastolic.

On April 25, 1935, laminectomy was performed from the sixth dorsal to the first lumbar segment, and four days later the anterior nerve roots were severed

from the ninth dorsal to the first lumbar segment, inclusive. The postoperative course was uneventful, and the patient was walking on the fourteenth day. All subjective complaints disappeared. The arterial blood pressure varied from 166 to 190 mm. systolic and from 98 to 118 mm. diastolic. The average pressure was 150 systolic and 100 diastolic fourteen months after the operation. The papilledema disappeared, the exudate in the retina was reabsorbed and the arterioles were not constricted. The basal metabolic rate was — 3.5 per cent ten weeks after operation.

Comment.—This was a case of malignant hypertension of short duration which advanced rapidly. The changes in the eyegrounds were marked and were the outstanding physical finding. The eyegrounds were normal nine months after operation. Five pairs of anterior nerve roots were severed. The patient recovered quickly from the operation, and all the subjective symptoms disappeared. A comparison of the level of the blood pressure when the patient was at rest in bed before the operation with that when he was up and about fourteen months after the operation showed that the pressure had fallen an average of 40 mm. systolic and 20 mm. diastolic. This man now lives an active outdoor life.

CASE 11.—A 26 year old man, a clerk, who was referred to this hospital by Dr. Edward Saunders, complained of the sudden appearance of a blind spot in his right eye three weeks previously. There was no familial history of hypertension. The patient had always considered himself to be healthy. For the past two months he had noted that he became fatigued easily and that he had slight dyspnea on exertion. Nocturia also had occurred in the past month. No signs or symptoms other than these had been observed. Examination by Dr. Francis Glazebrook disclosed that the patient had proteinuria and hypertension.

The patient was well developed and appeared healthy. Examination of the fundi showed that papilledema (3 diopters) was present. The disks were surrounded by large areas of hard, white exudate which had coalesced, and throughout the retinas were small patches of exudate. The vessels which sprang from the disk were completely obliterated at many points. The arterioles showed all stages of constriction and degeneration, with perivascular reaction. The veins were dilated, tortuous and in many places markedly compressed by the arterioles. A well developed stellate figure was present in the macular region. The thyroid gland was normal. The heart was markedly enlarged both to the right and to the left. Measurements from an x-ray plate showed a total transverse diameter of 17.2 cm., with the internal diameter of the chest 27.4 cm. The aortic shadow appeared prominent and tortuous on the plate. The cardiac rate was increased (92 beats per minute) and there was a gallop rhythm. The aortic and pulmonic second sounds were both markedly accentuated; no murmurs were heard. Just inside the nipple line in the fifth interspace a friction rub was heard. The peripheral vessels were thickened (grade 2) and slightly tortuous. The electrocardiogram showed that the T wave was negative in leads I and II and upright in III. The conduction time was 0.2 second. There was marked preponderance of the left ventricle, and the rhythm was normal. An x-ray plate of the skull showed the sella turcica to be normal in appearance. The arterial blood pressure varied from a maximum of 210 to 166 mm. systolic and from 152 to 110 mm. diastolic during twenty-two days of rest in bed. The average pressure for this period was 190 systolic and 124

diastolic. The Klein and Wassermann tests for syphilis were negative. The blood sugar value was 102 mg. per hundred cubic centimeters. The basal metabolic rate was —8 per cent.

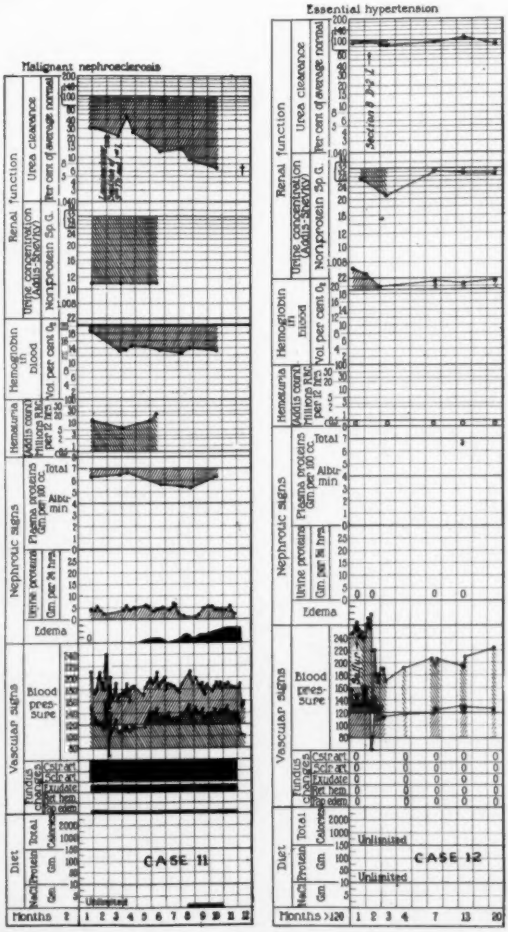

Fig. 7.—Case 11 was that of a man aged 26 with malignant nephrosclerosis. He was 182.5 cm. tall, and his ideal weight was 73.5 Kg. Case 12 was that of a woman aged 33 with essential hypertension. She was 153.5 cm. tall, and her ideal weight was 50.5 Kg.

On March 25, 1935, laminectomy from the sixth dorsal to the first lumbar vertebra was performed. Ten days later the anterior nerve roots were severed from the ninth dorsal to the first lumbar segment, inclusive. Recovery from the opera-

tion was uneventful. One month afterward measurements of the cardiac size from an x-ray plate showed a total transverse diameter of 16.5 cm., with the internal diameter of the chest 27.5 cm. The transverse diameter of the heart was 0.7 cm. less than before operation. The T waves in leads I and II, which had been negative, became upright, and the atrioventricular conduction time was reduced from 0.2 to 0.16 second. Five months after the operation an electrocardiogram showed upright T waves in all three leads, a conduction time of 0.16 second, preponderance of the left ventricle and a normal rhythm. The basal metabolic rate was —4 per cent twenty-two days after the operation. Five weeks after the operation the fundi of the eyes appeared little changed from their condition before operation, but five weeks later the papilledema had disappeared. The arterial blood pressure varied from 160 to 210 mm. systolic and from 98 to 142 mm. diastolic. The average was 184 systolic and 122 diastolic. The patient was discharged but returned three weeks later, exhibiting signs of cardiac failure. This quickly disappeared with the aid of rest in bed and digitalis. The renal efficiency was somewhat more reduced, and the blood pressure had risen almost to its preoperative level and at times above it. The patient was readmitted six months after operation, again with cardiac failure. The renal efficiency fell progressively. Death occurred from both renal and cardiac failure ten months after the operation.

Autopsy (by Dr. C. P. Rhoads).—The heart was markedly hypertrophied (weight, 695 Gm.), especially the left ventricle. Coronary sclerosis (grade 3) was present. The renal arteries showed atheromatosis and moderate thickening. Marked atheromatosis (grade 3) was found also in the aorta, and atheromatous plaques studded the larger cerebral vessels. There was marked hyaline thickening of the vessels of the spleen, liver and pancreas.

The capsule of the kidneys was stripped with difficulty, leaving a pebbled surface. The cortex was atrophied. Microscopic examination showed advanced changes in the renal vessels, consisting of thickening with hyaline connective tissue and with hyaline replacement of the muscular tissue. Some of the glomeruli appeared normal, others showed deposits of fibrin in the capillary loops and still others were occluded by masses of hyaline tissue, proliferation of the capsule and adhesions between tuft and capsule.

The bone marrow showed slight interference with maturation of the cells. Many young forms were present, with few adult cells.

Careful examination of the spinal cord showed that no regeneration of the severed anterior nerve roots had occurred. Histologic examination was made by Dr. Lewis Stevenson, who made the following report:

"Sections stained with cresyl violet show a considerable loss of anterior and lateral horn cells, together with severe changes in the cells which remain. These changes are, for the most part, those seen in retrograde chromatolysis, with swelling of the cell, eccentricity or absence of the nucleus and fragmentation of the Nissl granules.

"The Loyez myelin sheath stain shows an absence or a severe degeneration in the fibers running from the anterior horns to form the anterior root. Many of the fibers in the anterior roots can be seen with this stain to be lacking in myelin sheaths. In addition to this there is an unexpected degeneration in the white matter of the cord in the spinocerebellar tracts, to some extent in the pyramidal tracts and here and there throughout the posterior columns. There is thickening of the wall of the anterior spinal artery, with a narrowing of its lumen. There is complete thrombosis of one of the other arteries in the posterolateral portion of one side of the spinal cord. There is a thickening of the wall of many of the smaller arteries in the meninges about the cord. Sections of the cord stained with

Fig. 8 (case 11).—Section of the kidney showing marked vascular, tubular and interstitial changes. Eosin and methylene blue stain; × 60.

hematoxylin and sudan III show some compound granular corpuscles in the spinocerebellar tracts on both sides, the anterior horns being singularly free from fat or fat-containing cells. Sections of the spinal cord stained for neuroglia show no increase in astrocytes or neuroglia fibers. The sections stained for microglia show no increase in this element.

"The posterior roots stained for myelin appear to be normal. The anterior roots, on the other hand, stained by the same method show marked degeneration of the myelin sheaths. Sections of the anterior root stained with the Cajal stain show few normal axis-cylinders and an increase in the nuclei of the neurilemma.

"Because of the absence of proliferation of the neuroglia in the degenerated portions of the spinal cord a Masson trichrome stain was used, and this shows a considerable deposit of green-staining collagen replacing the degenerated fibers in the white substance of the cord and also, to some extent, in the anterior horns of the cord."

Comment.—This was a case of severe malignant hypertension, with a marked reduction in the renal efficiency. The exact time of onset cannot be stated, but the first symptom appeared only three weeks before the patient's admission to the hospital. Advanced morbid vascular changes had occurred and the heart and kidneys were seriously injured. The pathologic process in the kidneys was evidently active, because many red blood cells were being excreted as well as protein and large numbers of casts. We believed that the prognosis was hopeless and that death would not be long delayed. Only as a last resort was an operation performed. Five pairs of anterior nerve roots were severed in a two stage operation. For four months after the operation the patient continued to feel in excellent health. The average blood pressure fell 12 mm. systolic and 9 mm. diastolic, and the transverse diameter of the heart was reduced 0.7 cm. However, three months later there occurred cardiac decompensation, and there was evidence of further loss of renal efficiency. Both cardiac and renal failure progressed, terminating his life ten months after the operation. It was our opinion that the operation did not alter significantly the natural course of the disease. Autopsy confirmed the belief that morbid vascular change was widespread and severe. It proved also that after ten months no regeneration of the severed nerve roots had occurred. A corresponding loss of anterior and lateral horn cells was observed.

CASE 12.—A housewife 33 years old, referred to us by Dr. J. V. Bohrer, complained of nervousness and easy fatigability. Up to the time of the present illness she was in good health but highly excitable. She had been pregnant three times but had had an abortion performed each time. Ten years before her admission to the hospital (1925) the arterial pressure was 240 systolic and 150 diastolic and varied from 184 systolic and 110 diastolic to 234 systolic and 134 diastolic during the next year. It was 190 systolic and 140 diastolic two years later (1928), 200 systolic and 145 diastolic in 1929, 238 systolic and 140 diastolic in 1933 and 240 systolic and 150 diastolic in 1934. A year and a half before her admission to the hospital, her brother died, and shortly thereafter she became excessively nervous.

She cried without reason and blushed abnormally often. Except for emotional instability and ready fatigability there were no symptoms.

The patient was a well developed, overweight Jewess, who appeared nervous. Throughout the examination she was never quiet. The eyegrounds were normal. The thyroid gland was slightly and diffusely enlarged (grade 1). Marked systolic thrusts were observed in the suprasternal notch. The heart was only slightly enlarged. Measurements from an x-ray plate showed a total transverse diameter of 13.7 cm. and an internal diameter of the chest of 27 cm. The aorta was dilated (grade 2). There was a soft systolic murmur heard best to the left of the sternum in the fourth interspace and a second one heard over the base. The aortic second sound was slightly accentuated. The peripheral vessels were a little thickened. The deep reflexes were moderately hyperactive. Roentgen examination showed the sella turcica to be normal. An electrocardiogram exhibited a negative T wave in lead I, a diphasic T wave in lead II and an upright T wave in lead III, preponderance of the left ventricle and a normal rhythm. The renal efficiency was normal. The Kline test for syphilis was negative. The blood sugar value was 93 mg. per hundred cubic centimeters. The arterial blood pressure varied from 246 to 272 mm. systolic and from 132 to 150 mm. diastolic, averaging 258 systolic and 140 diastolic. Daily intramuscular injections of 2 cc. of colloidal sulfur produced no significant fall in the blood pressure. Even after the patient had spent five weeks in bed no reduction in pressure occurred, and the daily variations were surprisingly small.

On April 9, 1935, laminectomy was performed, and the anterior nerve roots were severed from the eighth thoracic to the first lumbar segment, inclusive. The postoperative course was uneventful.

Shortly after the operation the blood pressure varied widely but soon stabilized. During the next two months the systolic pressure varied from 170 to 200 mm. and the diastolic pressure from 104 to 128 mm., averaging 182 systolic and 116 diastolic.

Comment.—This is a rather unusual case of benign hypertension of at least ten years' duration in a young woman. Ten years before her admission to the hospital the arterial pressure was 240 systolic and 150 diastolic. In spite of continued high pressure, there was little evidence of cardiac, renal or vascular damage. The arterial pressure was fixed at a high level and was not influenced by rest, injections of sulfur or sedatives. Section of six pairs of anterior nerve roots was performed. The arterial pressure fluctuated widely for about fifteen days and then stabilized at an average level of 208 systolic and 126 diastolic for twelve months after the operation. The average pressure before the operation was 258 systolic and 140 diastolic.

Case 13.—A 46 year old man, a director of social work, referred by Dr. A. Tow and Dr. A. Fishberg, of New York, complained of easy fatigability for the past four years. Three of his sisters have moderate hypertension, and one brother had died of high blood pressure. This patient was ill with scarlet fever at the age of 3 years. He had always been overexcitable, highly emotional and impulsive. Sixteen years before his admission to the hospital his blood pressure was normal, but one year later it was 150 mm. Four years before his admission he noted that even moderate exertion caused extreme fatigue. Since then insomnia, irritability, loss of memory and a "sensation of pressure all over the body" had become increasingly

distressing. He had had a number of severe nosebleeds. Emotional instability was so marked that he was unable to adjust himself to his ordinary duties. One year before his admission to the hospital a hemorrhage was observed in the left fundus. Long periods of rest did not reduce the arterial pressure. He had complained of anginal pains in the past few months.

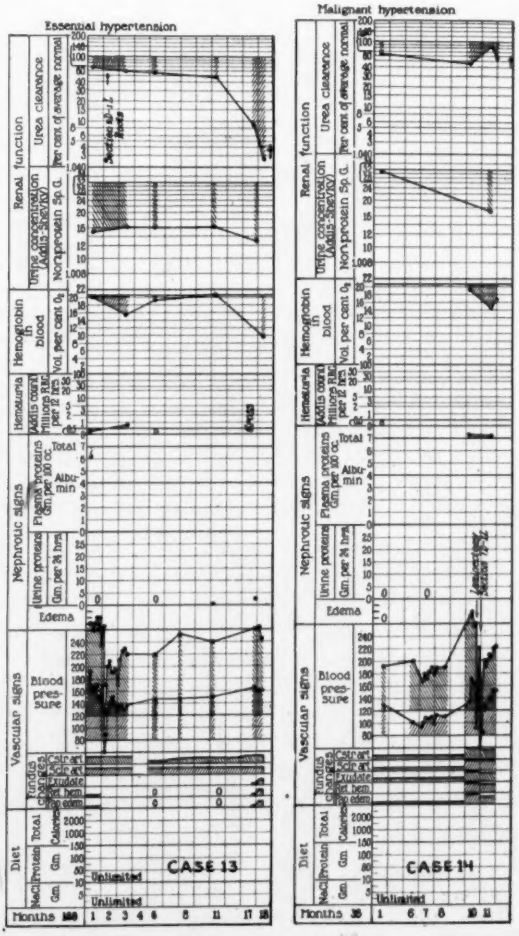

Fig. 9.—Case 13 was that of a man aged 46 with essential hypertension. He was 168 cm. tall, and his ideal weight was 60.3 Kg. Case 14 was that of a man aged 37 with malignant hypertension. He was 169 cm. tall, and his ideal weight was 64 Kg.

Physical examination showed a heavy-set middle-aged man, who did not appear ill but was restless and excited. The distribution of hair was normal. The disks

of the fundi were markedly hyperemic, and the edges were a little blurred. There was papilledema (grade 1). The arterioles were completely obliterated in many places, and some showed sausage-shaped constriction. They were tortuous (grade 3). The left inferior nasal artery was thrombosed. There was perivasculitis (grade 1) throughout the arteriolar tree and marked arteriovenous compression. The veins were moderately dilated and tortuous. In the left fundus there was a small flame-shaped hemorrhage, and throughout both fundi small areas of early exudate formation were seen. The heart was enlarged. Measurements from a roentgenogram showed a transverse diameter of 16.2 cm., with the internal diameter of the chest 27.5 cm. The aorta was tortuous and markedly dilated. The heart was boot shaped. The heart sounds were of good quality, and the aortic second sound was accentuated. The peripheral vessels were thickened (grade 2). All the reflexes were normal. The contour of the sella turcica was normal; the pineal gland was slightly calcified.

An electrocardiogram showed the T wave to be negative in lead I and positive in leads II and III. The auriculoventricular conduction time was 0.2 second, and preponderance of the left ventricle was present. Inhalation of a pearl of amyl nitrite reduced the arterial pressure from a control level of 250 systolic and 150 diastolic to a minimum of 204 systolic and 120 diastolic. Rest in bed with sedatives for thirty days did not reduce the arterial pressure significantly. During this period the pressure ranged from 232 to 280 mm. systolic and from 140 to 192 mm. diastolic, averaging 270 systolic and 160 diastolic.

On May 7, 1935, the anterior nerve roots were severed from the ninth thoracic to the first lumbar segment, inclusive. A moderate number of calcified plaques were found on the arachnoid membrane, and these made the operative procedure somewhat more difficult than usual. The blood pressure fell to 100 systolic and 70 diastolic, but the next day it rose to 170 systolic and 85 diastolic. Recovery from the operation was uneventful except for an episode suggestive of vascular collapse which occurred on the eighteenth postoperative day. Following a large defecation the patient felt weak and fainted. There were slight fever and leukocytosis, but no convincing evidence of coronary or pulmonary thrombosis was obtained. The arterial blood pressure fluctuated markedly for the first month after the operation but gradually stabilized at an average level of 240 systolic and 150 diastolic, with limits of from 220 to 260 mm. systolic and from 110 to 160 mm. diastolic. Slight regressive changes occurred in the eyegrounds, in that papilledema and the hemorrhage disappeared; otherwise they appeared to be unaltered. The size of the heart changed little. The vital capacity before operation was 3.4 liters, and seventeen days afterward it was 3.1 liters.

The patient lived an active and high strung life for the next sixteen months, when renal insufficiency rapidly appeared. He died seventeen months after operation. Autopsy showed that the vessels of most of the organs were markedly sclerosed. The kidneys in particular showed extensive vascular change.

Comment.—This patient had suffered from hypertension for fifteen years. The blood pressure had become "fixed" at a high level (averaging 270 systolic and 160 diastolic), for it was not lowered by rest in bed or sedatives. Vascular damage had occurred in the cardiac, retinal, renal and peripheral blood vessels. In spite of its seeming fixity, the blood pressure fell to 100 systolic and 70 diastolic shortly after operation. Five pairs of anterior nerve roots (ninth thoracic to first lumbar) were

severed. Recovery from the operation was uneventful. After a period of marked fluctuation the arterial pressure became stabilized at an average level of 240 systolic and 150 diastolic. Practically all subjective symptoms disappeared, especially the headaches. The patient resumed his former work and felt that he had been markedly benefited, in spite of the fact that the reduction in the average arterial pressure was not great. Death occurred seventeen months after operation, with extreme renal insufficiency. While marked subjective improvement occurred, it is not known whether the length of life was prolonged; if so, certainly not greatly.

CASE 14.—A 37 year old salesman, referred to us by Dr. C. Whiting, complained of severe headaches in the occipital region for the past two and one-half years. Five years before his admission to the hospital his blood pressure was normal. It was found to be 224 mm. fifteen months before admission. Three months later a hemorrhage occurred in the left fundus.

Physical examination showed extensive morbid changes in the eyegrounds. The heart was not overactive and was slightly if at all enlarged. On March 6, 1935, the total transverse diameter of the heart was 13.9 cm., and the internal diameter of the chest was 27 cm. The aorta was slightly dilated. An electrocardiogram showed only preponderence of the left ventricle at that time. The pineal gland was calcified, but the sella was normal. The blood pressure was 192 systolic and 130 diastolic. The patient was seen again nine months later; by this time the blood pressure had risen until it averaged 270 systolic and 170 diastolic with a maximum and a minimum systolic pressure of 280 and 262 mm. and a maximum and a minimum diastolic pressure of 186 and 160 mm., respectively. The papilledema was so intense that the nerve heads were literally mushroomed out into the posterior chamber. Hemorrhages and exudate were to be seen everywhere, except in the right eye, where the exudate was less extensive. The cardiac shadow was definitely enlarged, but much of the enlargement was due to widening and tortuosity of the aorta. Spinal puncture showed that the cerebrospinal fluid was under a pressure of 430 mm. of water. The cell count was not increased, but the protein content was definitely increased. In view of the remarkable rise in the arterial pressure and the advance in the morbid process in the eyegrounds, it was agreed that early fatal termination was probable. It was fully realized that operation was a last resort.

Laminectomy was performed on Dec. 23, 1935, from the fifth dorsal to the second lumbar vertebra, inclusive. On December 30 the nerve roots were sectioned from the seventh to the twelfth dorsal segment. The postoperative course was uneventful, and on the ninth day after the operation the patient was allowed up. Examination of the fundus one month later showed that the papilledema had markedly diminished. The other changes were so extensive that it was difficult to be certain whether there had been any change in them or not. Symptomatic relief was incomplete. The average arterial pressure was 210 systolic and 140 diastolic. Compound solution of iodine given in doses of 6 drops twice a day for fourteen days had slight, if any, effect on the rapid pulse rate. Two months after the operation the patient died with left hemiplegia.

Comment.—This was a case of advanced malignant hypertension, and operation was undertaken only as a last resort. The arterial pres-

sure fell from an average preoperative level of 270 systolic and 170 diastolic to 210 systolic and 140 diastolic. Marked recession of the papilledema occurred. Symptomatic relief was incomplete. While the immediate effects of the operation were beneficial, the progress of the disease was not halted.

CASE 15.—A 44 year old paper manufacturer, referred to us by Dr. T. Mackie, complained of headache and failing vision. There was a familial history of hypertension. The patient's health had always been excellent.

The patient had had repeated physical examinations, and until 1932 the blood pressure was normal. Shortly after that he began to have headaches, which had become more severe and frequent. The blood pressure was found to be slightly elevated, and after that it rose progressively. In January 1935 hemorrhages occurred in both eyes, with almost complete obliteration of the vision in the left eye. Headaches became more severe and at times were almost unbearable. Long periods of rest were not of any particular value either in relieving the headaches or in reducing the blood pressure.

Physical examination showed a well developed man, who did not appear ill. There was no evidence of the "diencephalic syndrome." Examination of the left fundus showed that the retina was almost completely obliterated with hemorrhage and exudate. Here and there a vein could be seen and an occasional arteriole, the latter being extremely contracted. The right eye also showed extensive retinal change. The arterioles were tortuous and frequently buried in the retinal bed. There was papilledema (grade 2). There were no fresh hemorrhages but considerable evidence of resorbing ones. The thyroid gland was not palpable. The heart was slightly enlarged on percussion. The heart rate was elevated, and the sounds were of good quality. An electrocardiogram showed evidence of myocardial damage. Measurements of the heart from a roentgenogram showed a total transverse diameter of 13.2 cm. The internal diameter of the chest was 28 cm., and the aorta showed a marked bulge. A roentgenogram of the skull showed that the sella turcica was large, and there appeared to be slight erosion of the posterior clinoid process. The pineal gland was calcified (grade 3). The cold-pressor test showed a markedly overactive response (a rise of 62 mm. systolic and 16 mm. diastolic). The arterial pressure over a period of nineteen days in bed varied from 168 to 222 mm. systolic and from 118 to 150 mm. diastolic. The average pressure was 200 systolic and 132 diastolic. In view of the extreme changes in the eyegrounds and the rapid progress of the disease, a diagnosis of malignant hypertension was made, and extensive laminectomy with section of the anterior nerve roots was advised as the only possible means of retarding the disease.

On Dec. 3, 1935, laminectomy was performed, and six days later the anterior nerve roots were severed on both sides from the eighth dorsal to the first lumbar segment, inclusive. The wound healed without difficulty, but the patient had a mental upset. For a time it appeared as though he had a true psychosis, but this gradually disappeared with the help of physical therapeutic methods and small amounts of sedatives. After three weeks he was himself again, and his progress was rapid. Two months after the operation there was definite improvement in the ocular fundi. Constriction of the arterioles had disappeared. There were no fresh hemorrhages or any new exudate. Slight papilledema was still present in

the right eye, and the old scar of the nerve head was visible in the left eye. The cold-pressor test showed a response of 28 mm. systolic and 26 mm. diastolic. There was no change in the renal efficiency. There appeared to be marked subjective

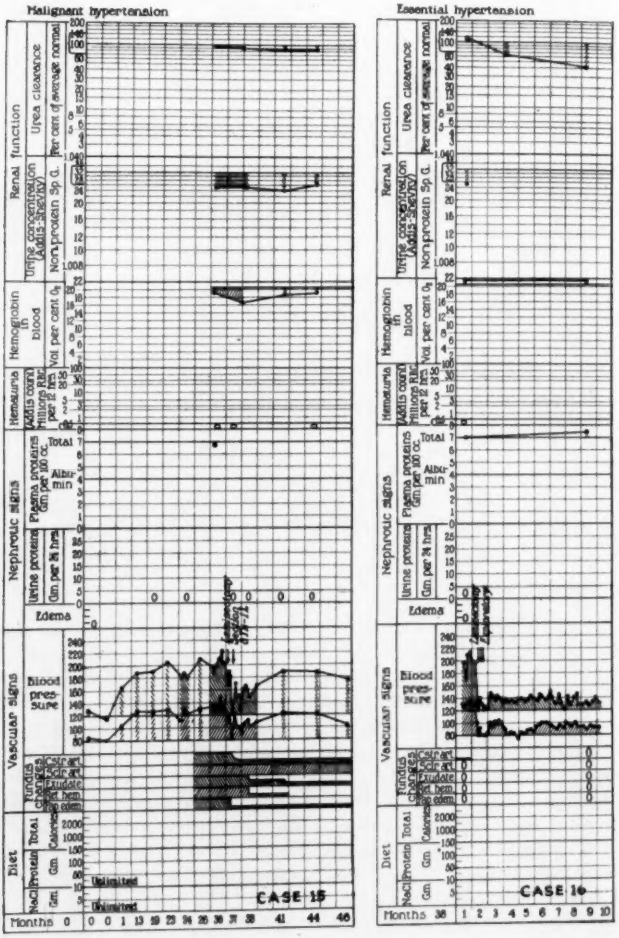

Fig. 10.—Case 15 was that of a man aged 44 with malignant hypertension. He was 175 cm. tall, and his ideal weight was 67.8 Kg. Case 16 was that of a man aged 21 with essential hypertension. He was 172 cm. tall, and his ideal weight was 66 Kg.

improvement. The arterial pressure varied from 130 to 194 mm. systolic and from 90 to 120 mm. diastolic. The average pressure was 186 systolic and 120 diastolic seven months after the operation.

Comment.—This was a case of severe malignant hypertension. Operation resulted in symptomatic relief. The arterial pressure fell from an average preoperative level of 208 systolic and 136 diastolic to 186 systolic and 120 diastolic. Marked regression in the morbid changes in the eyegrounds occurred. Thirteen months after operation the systolic blood pressure had risen to a level only slightly below the preoperative level, but the diastolic pressure was 30 mm. or more lower. It is our opinion that the rapid progress of the disease was markedly retarded but that the ultimate prognosis may be poor.

CASE 16.—A 21 year old man, referred to us by Dr. F. M. Hanes and Dr. E. L. Persons, of Durham, N. C., had no complaints. There was no familial history of hypertension.

This patient was impulsive and overexcitable, but from all outward appearances he seemed to be a perfectly normal college student. By chance during the course of a routine physical examination when he was 18 hypertension was discovered. The blood pressure two years later was found to be 200 systolic and 133 diastolic. The heart and eyegrounds were normal. The patient was admitted to a hospital, and the blood pressure was found to be 220 systolic and 152 diastolic. Other examinations, including the Wassermann and Kahn tests, revealed no abnormality. During the course of the year the heart was found to have enlarged. The basal metabolic rate was +7. An electrocardiogram was suggestive of myocardial damage, because the T waves in leads I and II were inverted, and the T wave in lead IV was diphasic along with a levogram. Fresh hemorrhages were found in the retina. Since there was no significant fall in the blood pressure and the pressure remained at a dangerously high level, he was referred to this hospital for examination.

Physical examination showed an unusually well built, well developed man who did not appear ill. The arterioles of the fundi showed sausage-shaped constrictions, but the retinas were otherwise normal. The heart appeared slightly if at all enlarged. The aorta was dilated (grade 2). The peripheral vessels were thickened (grade 1). A roentgenogram of the skull showed that the contour and density of the sella were normal. The response to the cold-pressor test was marked, the systolic pressure rising to 50 mm. and the diastolic to 48 mm. The arterial pressure varied from 170 to 210 mm. systolic and from 122 to 140 mm. diastolic, with an average of 200 systolic and 132 diastolic over a period of three weeks.

On Jan. 6, 1936, laminectomy was performed from the sixth dorsal to the second vertebra, inclusive. The following day the patient was paralyzed in both legs. The wound was opened, and a blood clot was removed, which may have been compressing the cord. Since an immediate return of function did not occur, the wound was reopened and the dura and cord were carefully inspected, but no abnormality was noted. After two months, slight sensation returned, and in four months there appeared to be slight voluntary movement. It is too early to predict how much function will return. The blood pressure has been markedly reduced, the average being 140 systolic and 100 diastolic.

Comment.—This was a case of relatively early essential hypertension in which the arterial pressure was rapidly rising and in which cardiac changes were already present. The fact that hemorrhages were observed

in the eyegrounds at one time suggests that the disease might be malignant. After operation transverse myelitis developed, possibly as a result of pressure from a blood clot. After two months slight sensation in the legs returned and after four months slight motor power. It is too early to be certain of the outcome of this serious accident. The arterial blood pressure has been sharply reduced.

CASE 17.—A 37 year old broker complained of severe headaches for the past eight years. In January 1928, during a casual examination, his blood pressure was found to be 145 systolic and 100 diastolic. Shortly following this, as a result of the stock-market crash, the patient went through a long period of intense overwork and worry. He became nervous and was unable to sleep. It was found that his blood pressure was slowly rising. In December 1931 Dr. George Crile performed bilateral adrenal denervation. The operation had no effect either on the symptoms or the level of the blood pressure. The patient gave up work entirely because of headaches and nervousness. He had some signs and symptoms of the "diencephalic syndrome."

Physical examination showed that the vessels of the eyegrounds were slightly constricted (grade 1) and a little tortuous in some places, but usually the course was normal. The heart was boot shaped and enlarged (grade 2). The peripheral vessels were thickened (grade 1). A roentgenogram of the heart showed that the total transverse diameter was 14.5 cm. and that the internal diameter of the chest was 26 cm. Of especial interest is the fact that the aorta was markedly and diffusely dilated. A roentgenogram showed that the sella turcica was normal. The blood pressure throughout the patient's stay of twenty-five days in bed averaged 230 systolic and 140 diastolic, the maximum and the minimum systolic pressure being 278 and 210 mm. and the maximum and the minimum diastolic pressure 150 and 120 mm., respectively. The cold-pressor test showed a response of 56 mm. systolic and 28 mm. diastolic pressure. The patient cooperated well in trying the "progressive relaxation" treatment. He learned a great deal from it, and we believe that the maximum fall in blood pressure that could be expected was obtained.

On Feb. 3, 1936, laminectomy from the sixth dorsal to the second lumbar vertebrae was performed. The postoperative course was uneventful, except that the patient refused to have the second stage of the operation performed, that is, have the dura opened and the nerve roots severed. Every effort was made to induce him to have the operation completed. He was up in a chair fourteen days after the operation. The arterial blood pressure soon rose to the preoperative level. Some symptomatic relief occurred, but it lasted only a few months.

Comment.—This was a case of essential hypertension with moderately disabling symptoms. Adrenal denervation performed elsewhere did not reduce the arterial pressure or relieve the symptoms. "Progressive relaxation" was tried with what appeared to be only moderate success. Laminectomy was performed, and for reasons of his own the patient refused to allow the second stage of the operation to be performed, i. e., exposure of the cord and section of the roots. He therefore voluntarily acted as a control for our series of cases. The arterial pressure soon rose to the preoperative level. Four months

after the operation it was above the preoperative level, and fresh hemorrhages, exudate and papilledema had appeared in the eyegrounds. When last heard from (seven months after the operation) the patient was obviously in the terminal phase of the disease.

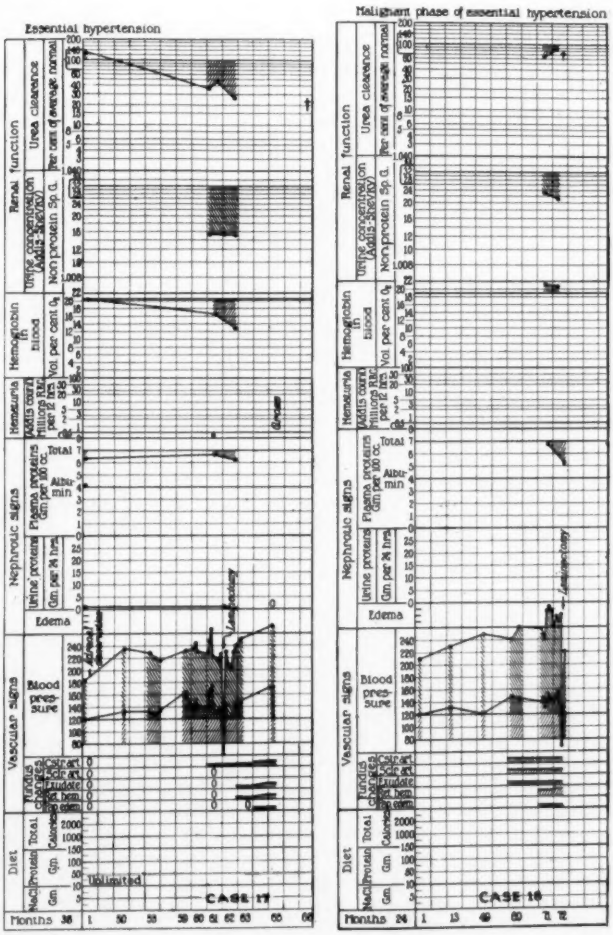

Fig. 11.—Case 17 was that of a man aged 37 with essential hypertension. He was 171.5 cm. tall, and his ideal weight was 70 Kg. Case 18 was that of a woman aged 39 with essential hypertension in the malignant phase. She was 148 cm. tall, and her ideal weight was 52.5 Kg.

CASE 18.—The complete history of this 39 year old woman will not be presented. She died as a result of septicemia due to the hemolytic streptococcus three days after laminectomy was performed. Hypertension had been discovered six months before she was admitted to the hospital. Fresh hemorrhages and exudates were observed in the ocular fundi, with papilledema. Moderate cardiac hypertrophy and dilatation of the aorta were noted. The renal function was slightly reduced (the urea clearance was 81 per cent of normal, and the maximum concentrating ability was 1.023). The average arterial pressure was 270 systolic and 148 diastolic over a period of five weeks while the patient was in bed.

Laminectomy was performed, but the dura was not opened. The following day it was observed that the patient's neck was stiff and that she was confused mentally. Almost complete anuria followed (the urea clearance was 4.2 per cent of normal). The extremities were pale and bloodless. Culture of the blood and spinal fluid showed the presence of hemolytic streptococci of group A (Lancefield).[28] Transfusions of blood and the intravenous injection of solutions of sodium lactate, sodium chloride and dextrose were associated with reestablishment of the urinary flow. The urea nitrogen content rose to a maximum of 83 mg. per hundred cubic centimeters of blood, and there was 15.24 millimols of carbon dioxide per liter of blood. The latter value rose to normal, and the urea nitrogen value fell. In spite of the reestablishment of more normal urinary function the patient passed into a coma and died three days after the operation.

Autopsy limited to the incision made at operation showed streptococcic meningitis. The adrenal glands appeared normal except for a small adenoma. The kidneys were swollen, pale and soft, and the line of division between the cortex and the medulla was indistinct. Culture of material from the cord showed group A hemolytic streptococci.

CASE 19.—This patient, a 22 year old housewife, had no complaints. In July 1929 her blood pressure was found to be normal. She was examined every six months thereafter until 1933, and the pressure was never found elevated. At that time she became pregnant, and during the course of pregnancy she was told that hypertension and proteinuria had developed. The pregnancy ended in a miscarriage. In October 1934 she was again pregnant. The blood pressure was found to be 280 mm. Severe headaches appeared.

Physical examination showed a well developed, slightly obese woman, who did not appear ill. Examination of the fundus revealed grade 3 constriction of the arterioles, many of them showing well defined sausage-shaped constriction. These vessels were slightly more tortuous than normal. The veins were dilated (grade 2). The physiologic cupping was unusually deep, and the nerve head was a little wider and more pale than normal. The heart did not appear to be laboring excessively. The sounds were of good quality. There was grade 1 to 2 enlargement. The aorta was markedly elongated and tortuous but not dilated. A roentgenogram of the skull showed that the sella was normal and that the pineal gland was not calcified. The cold-pressor test showed a maximum rise in systolic pressure of 20 mm. and in diastolic pressure of 10 mm. The renal efficiency was markedly reduced. The maximum and the minimum systolic blood pressure were 290 and 230 mm. (average, 260 mm.), and the maximum and the minimum diastolic pressure were 180 and 122 mm. (average, 160 mm.), respectively. During her stay in the hospital severe secondary glaucoma developed. It did not respond to treatment with hot compresses and physostigmine.

28. The streptococci were typed by Mrs. R. Lancefield.

Section of the anterior root was performed on April 25, 1936. The patient bore the operation exceptionally easily and on the ninth day was up and about. Shortly after the operation it was found that the intra-ocular tension in both eyes was normal. Examination of the fundi showed that the secondary glaucoma had entirely disappeared and that there was slight secondary atrophy of the nerve head in the left eye. The arterioles showed grade 2 constriction and in many places

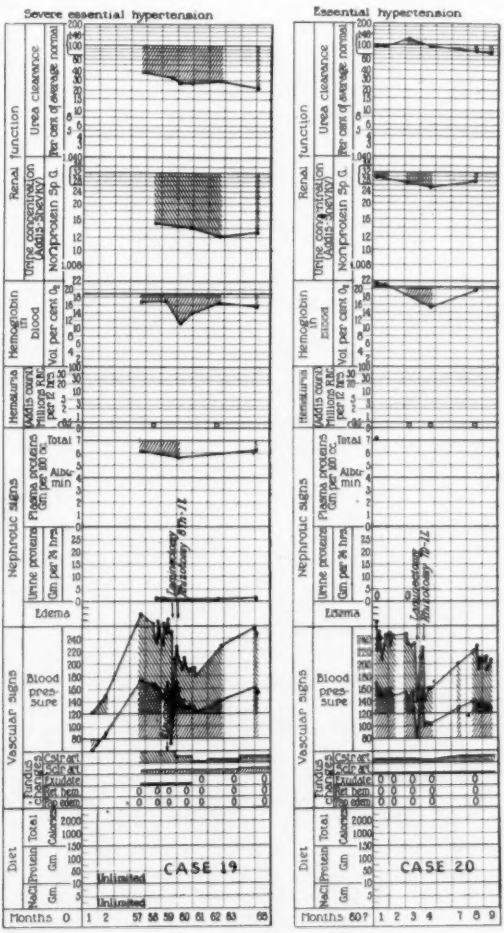

Fig. 12.—Case 19 was that of a woman aged 22 with severe essential hypertension. She was 167 cm. tall, and her ideal weight was 63 Kg. Case 20 was that of a man aged 40 with essential hypertension. He was 169 cm. tall, and his ideal weight was 64 Kg.

were tortuous. There were no hemorrhages, but there were points suggestive of an early hard, white exudate formation. The blood pressure fell to an average level of 192 systolic and 130 diastolic for a period of two and one-half months, but during the ensuing four months it rose to 256 systolic and 156 diastolic. The glaucoma has not reappeared, and the headaches occur only occasionally. It is apparent, however, that the beneficial effects of the operation as regards the blood pressure may be temporary.

Comment.—This was a case of severe essential hypertension beginning during pregnancy. The arterial pressure was persistently high (260 systolic and 160 diastolic) in spite of rest in bed and sedatives. Secondary glaucoma developed while the patient was receiving treatment in the hospital. Convalescence from the operation was exceptionally easy. The glaucoma and headaches disappeared immediately after the operation. The arterial pressure was reduced to an average of 192 systolic and 130 diastolic for two and one-half months, but nine months after the operation it had returned to an average level of 230 systolic and 142 diastolic. The beneficial effects of the operation may be only temporary.

CASE 20.—A 40 year old man had complained for at least a year of fatigue, dizziness and attacks during which unconsciousness occurred. Recently headaches had occurred sometimes lasting for three or four days. There have been no signs or symptoms of the "hypertensive diencephalic syndrome." Often he had pains just below the heart that caused him great alarm. One year before his admission to the hospital the blood pressure was found to range from 220 systolic and 150 diastolic to 158 systolic and 124 diastolic. Three months before his admission to the hospital he noticed for the first time transient paralysis of the left arm associated with unconsciousness which lasted for a few hours.

Physical examination showed a middle-aged man who did not appear ill. Examination of the fundus revealed that the nerve heads were hyperemic (grade 1). The arterioles were constricted (grade 2 to 3), with slight tortuosity and little perivascular reaction. There was slight arteriovenous constriction (grade 1), but no exudate or hemorrhage was present. There was a marked thrust in the jugular notch. Percussion showed the heart to be somewhat boot shaped. The heart sounds were of good quality. The aortic second sound was markedly accentuated. The peripheral vessels were thickened (grade 1). A roentgenogram of the skull showed a normal sella. The pineal gland was calcified (grade 1). The cold-pressor test showed a rise of 20 systolic and 26 diastolic. The maximum systolic pressure was 280 mm. and the minimum 156 mm. The maximum diastolic pressure was 164 mm. and the minimum 116 mm., with an average of 240 systolic and 150 diastolic. The fluctuations in blood pressure were wide.

Section of the anterior roots from the seventh thoracic to the first lumbar segment was performed on May 3, 1936. Nine days postoperatively the patient was up and feeling well. Examination of the fundi two weeks after the operation showed in some places grade 2 and 3 constriction, but the sausage-shaped constriction which was present before operation had disappeared. The patient had had no headaches. The cold-pressor test showed a systolic rise of 4 mm., and no diastolic rise. The average blood pressure was 210 systolic and 132 diastolic. At the time of his discharge the patient was considered to be improved.

Comment.—This was a case of severe essential hypertension in a middle-aged man. Attacks of unconsciousness with transient paralysis caused him great distress. Section of the nerve roots was well borne and was associated with a fall in the average arterial pressure from 240 systolic and 150 diastolic to 210 systolic and 132 diastolic. No attacks have occurred during the six months since operation.

BIOPSY OF MUSCLE REMOVED AT OPERATION

Dr. C. P. Rhoads examined the specimens removed from the lumbar muscles at operation and stated that, except in cases 2, 5 and 12, morbid changes in the arterioles were not seen. It is of interest to note that two patients with malignant hypertension and two with so-called "fixed" hypertension exhibited no significant morphologic changes.

COMPLICATIONS ASSOCIATED WITH THE OPERATION

While in most cases recovery from operation was uneventful, in a few serious difficulties occurred. One patient (case 9) died just after closure of the dura. She might have survived the two stage operation as it is now our custom to perform it. A second patient (case 18) died as the result of septicemia due to a hemolytic streptococcus three days after laminectomy was performed. The dura had not been opened. The streptococcus proved to belong to the Lancefield group A. We have been unable to ascertain the source of the infection. Since the operation was performed in February, at the height of the season for infections of the upper respiratory tract, it suggests that, if elective, operation should be postponed until infections are not prevalent.

Transverse myelitis with paralysis of both legs occurred in one patient (case 16) eighteen hours after the laminectomy. The dura was not opened. At a second operation a moderate amount of blood clot was removed which may have pressed on the cord. As recovery was not immediate, the dura was opened at a third operation, and the cord was carefully inspected. None of us could see any change in its appearance which was considered abnormal. Slight sensation in the legs has slowly returned, together with slight motor function. It is our belief at present that recovery will be only partial.

One patient (case 15) was irrational during part of each night for two weeks after the operation and then recovered fully. The operation appeared to be associated with the release of a flood of deeply suppressed thoughts. Physical therapeutic measures, such as warm baths, thermal light treatment and massage, were of value in quieting him.

COMMENT

Seventeen patients have been subjected to section of the anterior nerve roots. The character of the disease has varied greatly (table 1).

TABLE 1.—*Summary of the Clinical Data for Patients in Whom Section of the Anterior Roots Was Performed* *

Case	Sex	Age	Duration of Hypertension	Retinal Changes	Cardiac Changes	Urea Clearance, % of Normal	Blood Pressure Before Operation, Mm. of Mercury: Average	Maximum	Minimum	Number of Pairs of Anterior Nerve Roots Sectioned	Level of Roots Sectioned	Date of Operation	Blood Pressure After Operation, Mm. of Mercury: Average	Maximum	Minimum	Period of Observation After Operation, Months	Subjective Improvement
Group 1. Severe Benign Hypertension with Moderate Vascular Changes																	
12	F	33	>10 yr.	0	++	90	258/140	272/150	246/132	6	8Th-1L	4/ 9/35	182/116	200/128	170/104	5	Moderate
19	F	22	2 yr.	+++	+	31	260/160	290/180	230/122	6	8Th-1L	5/ 1/36	240/138	.....	.....	..	Marked
20	M	40	3 yr.	0	+	92	240/150	280/164	156/116	7	7Th-1L	5/ 4/36	160/116	180/134	154/110	2	Marked
Group 2. Severe Benign Hypertension with Marked Vascular Changes																	
6	F	40	>2 yr.	++	++	72	230/142	260/160	208/132	4	9Th-12Th	3/ 7/35	210/122	260/146	180/110	10	Marked
7	F	35	>3 yr.	+	+	88	190/122	212/132	182/108	6	7Th-12Th	1/25/35	176/114	200/120	160/ 98	4	Marked
13	M	46	15 yr.	+++	++	68	270/160	280/192	232/160	5	9Th-1L	5/ 7/35	230/142	250/150	220/110	10	Marked
Group 3. Hypertension in Young Women Exhibiting the "Hypertensive Diencephalic Syndrome"																	
1	F	23	>18 mo.	0	0	104	190/122	200/140	162/108	9	6Th-2L	5/11/34	150/ 96	170/104	110/ 70	29	Very marked
2	F	24	±2 yr.	+	0	80	106/149	220/160	180/130	5	9Th-1L	11/ 2/34	162/ 98	180/112	120/ 80	16	Very marked
3	F	17	18 mo.	+	0	106	180/122	210/144	136/ 94	5	9Th-1L	12/18/34	140/ 90	152/100	122/ 70	19	Very marked
4	F	32	8 yr.	0	0	101	210/130	230/145	176/126	5	9Th-1L	11/30/34	154/104	186/120	140/ 92	15	Marked
5	F	25	3 yr.	+	0	91	184/116	264/148	148/ 90	9	6Th-2L	10/29/34	156/106	170/120	140/ 90	12	Marked
8	F	25	2 yr.	++	+	74	210/130	240/138	170/112	6	8Th-1L	1/ 7/35	182/118	220/128	120/ 90	13	Marked
Group 4. Malignant Hypertension																	
9	F	26	>1 yr.	++++	++++	18	200/110	212/114	170/ 90	7	6Th-12Th	6/20/34	Patient died shortly after the dura was closed				
10	M	24	7 mo.	++++	+	92	190/120	232/132	182/112	5	9Th-1L	4/25/35	150/100	190/118	146/ 98	14	Marked
11	M	26	±3 mo.	++++	++++	30	190/124	210/152	166/110	5	9Th-1L	3/25/35	190/138	210/154	160/ 98	10	No symptoms present before operation
14	M	37	>2 yr.	++++	++	55	270/170	280/186	262/160	6	7Th-12Th	12/30/35	210/140	222/156	190/120	1	Moderate
15	M	44	3 yr.	++++	++	88	208/136	222/150	168/118	6	8Th-1L	12/ 3/35	186/120	190/122	140/ 90	7	Marked
Group 5. Patients in Whom Laminectomy but Not Root Section Was Performed																	
16	M	21	2 yr.	0	+	119	200/132	210/140	170/122	0	.....	1/ 6/36	140/100	150/114	110/ 70	8	No symptoms before operation
17	M	37	7 yr.	+	+	42	230/140	278/150	210/120	0	.....	2/ 3/36	240/146	260/154	220/130	4	Questionable
18	F	39	6 yr.	+++	+	86	270/148	290/160	230/132	0	.....	2/19/36	.....	.....	.....	..	Died of streptococcic meningitis

* The cases are grouped according to the character of the disease.

In one the disease was moderately benign but of long standing; in some it was of short duration and highly malignant, while in others, besides hypertension, a reduction in the renal efficiency was marked ("nephrosclerosis"). The results of operation are correspondingly not comparable within the entire group.

Three patients (cases 12, 19 and 20) showed severe but benign involvement, with moderate vascular change. There was variation as to the rate at which the morbid process was advancing. The arterial pressure was uniformly unusually high, yet symptoms were not especially marked. In one patient (case 19) severe secondary glaucoma developed, and one (case 20) had a series of attacks resembling transient apoplexy. Section of the roots in these cases has produced benefit, although it appears to be temporary.

Six patients (cases 1 to 5 and 8) exemplify a type of hypertension commonly found in young women. All were less than 32 years of age. Renal and cardiac changes were minimal, but constriction of the retinal arterioles was easily observed. Symptoms such as headache and shortness of breath were present and usually severe. Especially marked were symptoms which have been grouped under the term hypertensive diencephalic syndrome.[29] Section of from five to nine pairs of nerve roots resulted in a pronounced fall in the arterial pressure. Many of the subjective symptoms disappeared, especially headache and palpitation. The "diencephalic symptoms" were less obviously influenced. This group of patients appeared markedly benefited.

Three patients (cases 6, 7 and 13) suffered from benign essential hypertension of long duration. Evidence of marked vascular change was found on examination of the eyegrounds and the peripheral vessels and in the sections of muscle removed at operation. Cardiac changes were present, as shown by the electrocardiograms, the roentgenograms and the symptoms and signs which developed when the heart was under slight strain. The renal efficiency, as estimated by the ability to concentrate urine and the urea clearance test, was moderately reduced. The arterial pressure, especially the diastolic, was regularly high. The diastolic pressure was as high as 192 mm. in one patient (case 13). Four pairs of nerve roots were severed in one patient (case 6), five pairs in another (case 13) and six pairs in the last (case 7). The arterial pressure fell definitely but by no means to normal. Subjective improvement was marked. The patient (case 6) in whom only four pairs of roots were cut died of apoplexy nine months after the operation. The other (case 13) actively engaged in his business for a year but died with renal insufficiency seventeen months after operation. The

29. Page, I. H.: A Syndrome Simulating Diencephalic Stimulation Occurring in Patients with Essential Hypertension, Am. J. M. Sc. **190**:9, 1935.

last patient is doing well two years after operation. It is our opinion that the reduction of pressure from such excessively high levels may reduce the strain on the heart and blood vessels sufficiently to prolong life somewhat but that only in exceptional cases are the risks of operation justified.

The last group, consisting of three young and two middle-aged patients (cases 9, 10, 11, 14 and 15), had highly malignant types of hypertension. The disease was of short duration, but within this period the vascular damage was extreme. Marked neuroretinopathy was present in all these patients. In two the cardiac and renal changes were advanced, in two they were moderate, and in one they had just appeared. Five pairs of anterior nerve roots were severed in each of two patients (cases 10 and 11), six pairs in two (cases 14 and 15) and seven pairs in the other (case 9). One patient (case 9) died shortly after closure of the dura. Autopsy showed no hemorrhage in the cord but a persistent thymus gland and marked cardiac and renal damage. The cause of death was not definitely established, though shock seems possible. The second and third patients (cases 10 and 15) appeared to be benefited by the operation, in that the subjective symptoms disappeared and a marked regression in the morbid changes in the eyegrounds and a significant fall in blood pressure occurred. The fourth and fifth patients (cases 11 and 14) did not appear to be aided. Cardiac decompensation occurred in one, and the level of the blood pressure was at times as high as before operation. The renal function and hemoglobin content steadily diminished. It was our opinion that the natural course of the disease had not been altered. The other patient died of apoplexy.

A number of our patients exhibited so-called "fixed" hypertension; that is, the blood pressure remained high and showed little variation in spite of rest and sedatives. During operation the arterial pressure of these patients fell as markedly as in those with "labile" hypertension. In all of them it remained low long after the effects ordinarily associated with a major operation had passed off. No symptoms or signs of cardiac insufficiency were present. Consequently, although morbid changes had occurred in some of the blood vessels which were examined, either enough uninjured vessels remained which could dilate, or those vessels which appeared to be injured had not lost this power. Evidence is insufficient to decide which of the two explanations is correct. It seems important to lay stress on the observations that dilatation of blood vessels sufficient to lower the arterial pressure can occur in a patient in whom organic change in the vessels was believed to fix the arterial pressure at a high level.

Summarizing the effect of section of the anterior nerve roots on the level of the arterial blood pressure in patients who have been studied for from six to twenty-nine months after operation, the following general

statement may be hazarded: Group 1: Those patients in whom the disease is benign but in whom advanced vascular change has not occurred may respond well. Group 2: In cases of more advanced, longstanding involvement with morbid vascular change but with a benign character a favorable result may occasionally be obtained. Group 3: Young patients exhibiting symptoms and signs of the "diencephalic syndrome" may respond in a satisfactory manner. Group 4: Patients suffering from highly malignant hypertension rarely respond favorably.

Observation of patients following operation shows clearly that in groups 2 and 4 the arterial pressure may remain markedly reduced for periods up to six months but that a slow rise then usually occurs until the preoperative level is nearly reached. The subjective improvement of most patients was so marked that they felt the operation was justified. As the therapeutic effects, both subjective and objective, are more evident in groups 1 and 3, further investigations employing this or other simpler operative procedures appear warranted. The tendency for the arterial pressure to return to its preoperative level has been much less definite. It must be remembered, however, that the period of postoperative study has been only two and one-half years in the latter groups; hence, great caution is necessary in evaluating the effects of the operation on the natural history of the disease.

The normal level of urea clearance before operation in our cases of hypertension makes it appear probable that the renal blood flow in these cases was merely normal and not elevated by the hypertension. This is based on the observation of Van Slyke, Rhoads, Hiller and Alving [21] that in dogs the urea clearance parallels chiefly the renal blood flow. It appears probable that the same parallelism occurs in patients.

It has been shown [1] that an abnormal elevation of the arterial pressure in cases of essential hypertension or nephritis does not appear to assist in the maintenance of renal efficiency. The values for the urea clearance obtained when the blood pressure was high were compared with those obtained after the pressure was reduced entirely or partly to normal, either spontaneously or as the result of injections of sulfur, the administration of sodium thiocyanate or a major operation. No fall in the clearance accompanied the observed decreases in the blood pressure. Data in this paper offer additional evidence of the same nature, for a marked reduction in the arterial pressure followed the operation of section of the anterior nerve roots without significant change either in the urea clearance or in the ability to concentrate urine.

Renal denervation by means of stripping the renal pedicle does not alter the urea clearance in cases of essential hypertension or nephritis,[30]

30. Page, I. H., and Heuer, G. J.: The Effect of Renal Denervation on the Level of Arterial Blood Pressure and Renal Function in Essential Hypertension, J. Clin. Investigation **14**:27, 1935. The Effect of Renal Denervation in Patients Suffering from Nephritis, ibid. **14**:443, 1935.

and, as the kidneys are partially denervated as the result of the operation of section of the anterior nerve roots, observations on patients subjected to this operation are comparable to those following stripping of the renal pedicle. Again no change in the urea clearance was observed as a result of the denervation.

It appears that changes in the blood flow in the kidneys may occur independently of the extrinsic nerve supply.[30] The kidneys show a degree of vascular autonomy comparable to that of the brain. The fact that the caliber of the renal vessels may vary without assistance from the extrinsic nerve supply does not, however, prove that the nerve supply plays no part in their control.

Proteinuria and hematuria were insignificant in all the patients except two (cases 9 and 11) of those suffering from malignant hypertension. The hemoglobin value usually was temporarily reduced as a direct result of the operation, but this was soon corrected. Iron (1 Gm. three times a day) has been employed to aid in its regeneration. The plasma proteins were uninfluenced by the operation.

Except for an occasional reduction in the intensity of the papilledema, the most striking change in the fundi apparently resulting from the operation was relaxation of the constricted retinal arterioles. In two patients (cases 10 and 15) absorption of the hard, white exudate was observed. Secondary glaucoma disappeared in one patient (case 19).

Changes in the size of the heart, as measured by the shadow on an x-ray plate, and changes measured on the electrocardiogram, are summarized in table 2. Preponderance of the left ventricle was present in all the patients, and the atrioventricular conduction time varied from 0.12 to 0.2 second. In two cases (cases 11 and 13) significant reduction occurred after the operation (0.2 to 0.16 second). In a few of the patients (case 1, 2, 8, 11, 12 and 13) the size of the cardiac shadow on x-ray films was slightly reduced (fig. 13), while in the remainder no significant change was observed. Alterations of the electrocardiograms were not considered significant.

Besides the fall in the arterial pressure, the disappearance in subjective symptoms was striking. This cannot confidently be attributed entirely to the effects of operation in lowering the blood pressure. Certainly a major operation in conjunction with a prolonged period of rest in bed before the operation tends to reduce emotional instability.

It was of interest to observe that the "hypertensive diencephalic syndrome" did not disappear in some of the patients. Briefly, this syndrome, as described by one of us (I. H. P.),[29] consists of the spontaneous appearance of a mottled blush over the face and the upper part of the chest, both front and back, sweating, lacrimation, palpitation, a

slight rise in blood pressure, occasionally increased peristalsis and primitive emotional behavior. The basal metabolism may be normal. Blushing, sweating, lacrimation and palpitation are most often observed. Similar groups of signs and symptoms may occur in patients other than those suffering from hypertension, yet its frequent occurrence in

TABLE 2.—*Summary of the Electrocardiographic Changes and the Changes in the Size of the Heart as Observed Roentgenographically*

Case	Time in Relation to Operation	Time, Weeks	Electrocardiographic Changes: T Wave, Leads I	II	III	Other Changes	Time, Weeks	Transverse Diameter of Heart, Cm.	Internal Diameter of Chest, Cm.
1	Before	8	+	+	±	R III split; low voltage	2	12.9	23.0
	After	88	+	+	+		84	12.4	24.0
2	Before	2	+	+	−	.....	2	10.5	22.0
	After	64	+	+	+		40	10.2	23.5
3	Before	4	+	+	−	.....	4	10.1	23.5
	After	60	+	+	±	Q III	60	10.6	23.8
4	Before	1	+	+	−	.....	3	10.6	23.6
	After	60	+	+	+		44	10.6	22.7
5	Before	2	+	+	+	P III diphasic	3	12.0	25.0
	After	68	+	+	+		24	12.1	25.0
6	Before	2	+	+	−	.....	2	14.8	26.0
	After	24	+	+	−		28	14.4	26.0
7	Before	2	+	+	+	Deep Q III	2	11.8	25.0
	After	12½	−	+	+	Deep Q III	17	11.8	26.0
8	Before	3	+	+	−	.....	2	12.6	23.0
	After	52	+	+	−		50	11.2	24.1
9	Before	8	−	+	+	R II notched	..	....	....
10	Before	2	+	+	−	High voltage Q R S	2	13.1	26.0
	After	37	+	+	−	Q III	20	13.2	27.5
11	Before	2	−	−	+	.....	2	17.2	27.4
	After	20	+	+	+		4	16.5	27.5
12	Before	2	−	±	+	.....	3	13.7	27.0
	After	44	−	+	+		23	13.2	28.0
13	Before	1	−	+	+	.....	1	16.2	27.5
	After	40	±	+	+	P III split	20	15.0	27.5
14	Before	2	+	−	−	Q R S split in leads II and III	2	13.2	27.7
	After	4	+	+	−				
15	Before	2	±	±	−	P III diphasic	4	13.2	29.0
	After	3	+	+	+		32	13.1	29.2
16	Before	..	+	+	+	.....	3	13.7	29.8
17	Before	1	−	−	+	.....	3	14.5	26.0
	After	8	−	−	+	P II split			
18	Before	2	−	+	+	Q R S high voltage; P III diphasic	2	13.1	25.5
19	Before	10	+	+	+	.....	4	13.7	26.0
	After	..	..	..	..		8	14.6	26.5
20	Before	12	−	+	±	.....	4	14.0	27.0
	After	1	+	+	+	P III diphasic	5	13.7	28.2

hypertensive patients suggests some intimate association with the mechanism of the disease. Should it be proved that the "hypertensive diencephalic syndrome" is indicative of irritation of the vegetative centers in the brain, some clue to the etiology of essential hypertension might be obtained from a closer study of it. Since it occurs in certain patients (cases 2 to 4) in characteristic form in spite of a reduction in the blood pressure, it may be concluded that elevation of the pressure does not cause it.

Of especial interest from the point of view of the mechanism of the reduction in blood pressure is case 17, since the patient of his own choice acted as a control. Laminectomy was performed, but the second stage of the operation, namely, opening the dura and severing the nerves, was refused. Because of the nature of the disease and this patient's response to it, we believed that a favorable result was to be expected from surgical treatment. A marked reduction in the blood pressure occurred for a short period after the operation, but the pressure soon rose to its original level, indeed above it. Had the shock of operation been responsible for the prolonged lowering of the blood pressure which was observed in some of the other patients, it might

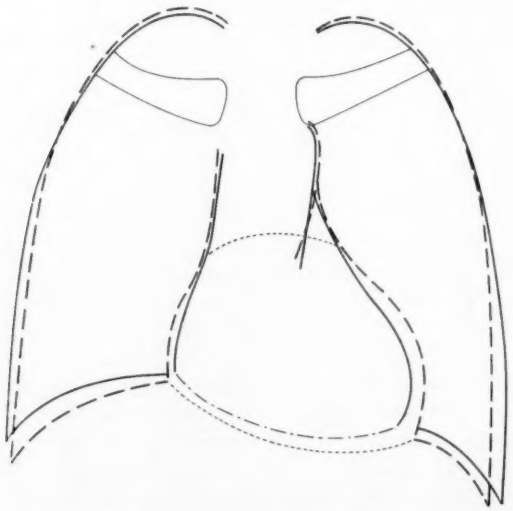

Fig. 13 (case 8).—Example of a decrease in the size of the heart following operation. The broken line represents the shadow on the roentgenogram before the operation (Nov. 26, 1934), and the continuous line represents the shadow seen fourteen months later (Jan. 21, 1936). Planimeter measurements of the cardiac area were 102.5 sq. cm. preoperatively and 86.4 sq. cm. postoperatively.

have been anticipated that the arterial pressure in this patient also would have remained at the lower level.

In contrast to this case is case 16, in which transverse myelitis occurred at the eleventh dorsal segment. The arterial pressure was reduced and has remained at the lowered level for eight months.

Opinion differs among investigators regarding the participation of the nervous system in the genesis of the hypertonus of the blood ves-

sels responsible for hypertension. The fact that prolonged reduction of the arterial pressure occurs following section of anterior spinal nerve roots suggests that the hypertonus is at least in part due to vasoconstrictor impulses. But it does not indicate whether these impulses are increased in frequency and intensity or are normal. Since in some patients the pressure tends to return to the preoperative level after a greater or lesser period of time, it is conceivable that either an insufficient vascular bed has been denervated or, as seems more reasonable, that some peripheral mechanism functions to cause hypertonus.

Associated with the question of the return of the blood pressure to its preoperative level is the problem of regeneration of the nerve roots. Although regeneration of the nerve ends after severance between silk ties might seem improbable, nevertheless it is a possibility. That it did not occur within a period of ten and seventeen months, respectively, is proved by case 11 and case 13. Careful examination of the cord at autopsy failed to show any regeneration.

Adson and Brown,[20] the originators of this operation, have published their results obtained in twenty-seven cases in preliminary form and one case in detail. The longest period of observation after operation was five years. The patient was a man with malignant hypertension. The blood pressure fell markedly and remained at levels from 140 to 166 mm. of mercury systolic and 80 to 110 mm. diastolic for a year and a half. Postoperative bleeding developed, which necessitated opening the wound. This was followed by weakness of the legs. Brown, Craig and Adson reported [31] that their studies were carried out from three to six weeks after operation. The mean values for the systolic pressure were 44 mm. systolic and 38 mm. diastolic less than before operation. The average reduction in the cold-pressor response (Hines-Brown test) was 80 mm. systolic and 45 mm. diastolic. When the patient was recumbent the arterial pressure was higher than when he was upright. Definite relaxation of the retinal arterioles occurred in some cases. Regression of retinitis was noted two or three weeks after the operation. Pain in the legs, which persisted for two weeks or more after the operation, was complained of by three patients. There was usually some subjective hyperesthesia of the skin of the thighs. A diminution in the transverse diameter of the heart was demonstrated after the operation in two cases.

Brown, Craig and Adson made the following statement: "Subjects less than 50 years of age, who have a relatively short history of hypertension, who present a serious prognosis, who have adequate function

31. Brown, G. E.; Craig, W. McK., and Adson, A. W.: The Treatment of Severe Essential Hypertension: Effects of Surgical Procedures Applied to the Sympathetic Nervous System, Minnesota Med. **18**:134, 1935.

of the kidneys, and in whose blood pressure reactions there is a large spastic element, as demonstrated by the excessive response to cold, and to emotional and other stimuli, are primary requisites" in the selection of patients for operation. These careful observers stated with wise judgment that "the ultimate value of this operation on the course and progression of these serious types of hypertension is not known."

Our experience confirms to a large extent that of Adson, Craig and Brown.[32] Although in some cases the arterial pressure has risen after a period of months to higher levels it has not returned to the preoperative level. In those cases in which the average arterial pressure was not greatly lowered as the result of the operation there was a return to the preoperative level within a few weeks. None of our patients complained of pain in the legs following the operation. We agree with Brown, Adson and Craig that it is too early to be certain of the ultimate effect this operation will have on the natural course of the disease. It is our opinion that some of the patients have markedly benefited both subjectively and objectively (in two and one-half years), even though perhaps temporarily, that others have been benefited subjectively and that others have received no benefit but have not been harmed by the operation. We do not regard the operation as an established therapeutic procedure even in those cases in which the benefits have been most marked. Disability resulting from the operation has not been observed in any of the patients except when complications have been encountered.

Since the operation is a major surgical procedure with a number of inherent risks, the results must be judged most critically for a relatively small number of patients before there can be any justification of its employment for large numbers of patients. It was with this purpose in mind that the present investigation was undertaken.

SUMMARY

Evidence of varied nature indicates that, as part of a more generalized vasoconstriction, vessels of the splanchnic area are narrowed in patients suffering from essential or malignant hypertension. Since no contraindications are known for reduction of the arterial pressure in such patients and there is no known medical treatment of more than temporary value, it appears to be justified to attempt to abolish the extrinsic vasomotor control of this area by section of the anterior nerve roots with the hope of reducing the arterial pressure. It has seemed desirable also to learn more of the part played by the nervous

32. Adson, A. W.; Craig, W. M., and Brown, G. E.: Surgery in Its Relation to Hypertension, Surg., Gynec. & Obst. **62**:314, 1936.

system in the genesis of hypertension. To this end seventeen patients have been subjected to the operation of section of the anterior nerve roots.

No attempt was made to select patients in whom in our opinion a favorable outcome might be anticipated. Six patients showed benign involvement of long duration, three of them with moderate vascular changes and three with severe changes. Six were young women with signs and symptoms of the "hypertensive diencephalic syndrome." Five suffered from highly malignant hypertension. The results of operation are therefore not comparable except within the subgroups.

While the ultimate effect of this operation on the natural course of hypertension cannot be foretold, from a study of these patients for periods of from eight to thirty-seven months after operation, the following results may be listed: (*a*) Three patients in whom the disease was severe but still benign and without advanced vascular change responded well. (*b*) One of three patients with more advanced involvement of long standing, with marked sclerotic but benign vascular changes, responded favorably. The headaches were relieved in the second and third cases, but the progress of the disease was unchecked. (*c*) Six young patients exhibiting the "hypertensive diencephalic syndrome" appeared benefited. (*d*) Three of those suffering from highly malignant hypertension were unaided by the operation, and two appeared to be improved. The favorable responses have been a marked, prolonged lowering of the arterial pressure, the remission of such symptoms as headache, pressure in the head and easy fatigability and marked improvement in the disposition. Other evidence of improvement in some of the patients has been relaxation of the spasm of the arterioles in the retina (eleven cases), absorption of exudate (two cases), disappearance of papilledema (three cases) and secondary glaucoma (one case), slight reduction in the size of the cardiac shadow in the roentgenograms (eight cases) and reversal of the T wave from the inverted to the upright position in lead I (two cases). There has been a definite tendency for a slow rise in pressure to occur over a period of two and one-half years in most but not all patients. Judgment must therefore be reserved as to the ultimate effects of the operation on the natural history of the disease.

Although marked anatomic change was present in the vessels of some of the patients, this did not prevent a marked fall in the arterial pressure, which persisted long after the patient had recovered from the immediate effects of the operation. This demonstrates that anatomic changes in the vessels do not account for the persistence of hypertension.

Renal efficiency, as measured by the urea clearance and the ability to concentrate urine, was unchanged either by the partial denervation of the kidneys which resulted from the operation or from the fall in blood pressure.

In those patients exhibiting the "hypertensive diencephalic syndrome" a marked lowering of the blood pressure did not cause it to disappear. If this syndrome is the somatic expression of irritation of vegetative centers in the brain stem and is not abolished by a reduction of the arterial pressure, it is probably not caused by elevation of the arterial pressure.

The operation of laminectomy does not of itself reduce the arterial pressure for more than several weeks. Transverse myelitis at the eleventh thoracic segment reduces it for prolonged periods (one patient was studied for nine months). These observations, with those concerning the effect of section of the anterior spinal nerve roots on the arterial blood pressure, suggest that the nervous system plays some part in the genesis of hypertension.

Although the operation has markedly improved the clinical condition of many of the patients studied for periods up to two and one-half years, its ultimate value in the *treatment* of hypertension has not been established.

RECKLINGHAUSEN'S NEUROFIBROMATOSIS

CLINICAL MANIFESTATIONS IN THIRTY-ONE CASES

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In a study of Recklinghausen's neurofibromatosis, a system disease, one is immediately impressed with (1) the lack of a known etiologic factor, (2) the apparent widespread differences of the various clinical types and (3) the lack of any known beneficial treatment. Though a great number of isolated cases have been reported,[1] there has been com-

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1. Weber, F. Parkes, and Boch, O. B.: Recklinghausen's Neurofibromatosis with Unilateral Buphthalmus and Multiple Changes in the Face and Skull, Proc. Roy. Soc. Med. **27**:638-640 (April) 1934. Marshall, W., and Watt, A. W.: A Case of von Recklinghausen's Disease, with Note on Psychology, Brit. M. J. **1**:234-235 (Feb. 10) 1934. Sykes, E. M.: Neurofibroma of Orbit of von Recklinghausen's Disease, Texas State J. Med. **29**:447-449 (Nov.) 1933. Sanford, J. A., and Thomas, E. P.: Von Recklinghausen's Disease with Unusual Distribution of Neoplastic Nodules, South. M. J. **26**:892-894 (Oct.) 1933. Lentaker, R. J., and Ward, J. H.: Neurofibromatosis with Report of a Case, U. S. Nav. M. Bull. **31**:301-305 (July) 1933. Hankey, G. T.: Von Recklinghausen's Disease with Local Tumor of the Palate, Proc. Roy. Soc. Med. **26**:959-961 (June) 1933. Wayson, J. T.: Multiple Fibromas: Recklinghausen's Disease, Arch. Dermat. & Syph. **27**:421-423 (March) 1933. Amerod, F. C.: Bilateral Auditory Nerve Tumor in a Case of Multiple Neurofibromatosis: Case, Proc. Roy. Soc. Med. **26**:566-567 (March) 1933. Knapp, A. A.: Von Recklinghausen's Disease: Case Presenting Involvement of the Left Eyelids, J. A. M. A. **100**:494-495 (Feb. 18) 1933; Multiple Neurofibromata of Acoustic Nerve, Brain and Spinal Cord (Cabot Case), New England J. Med. **208**:849-851 (April 20) 1933. Else, J. E.: Von Recklinghausen's Disease, with Tumor of the Spinal Cord, S. Clin. North America **13**:25-27 (Feb.) 1933. Kass, I. H.: Neurofibromatosis of the Bladder, Am. J. Dis. Child. **44**:1040-1047 (Nov.) 1932. Lightwood, R.: Naevo Neurofibromatosis, Proc. Roy. Soc. Med. **25**:1738 (Oct.) 1932. Corsi, H.: A Rare Type of von Recklinghausen's Disease, ibid. **25**:1739 (Oct.) 1932. Scarff, J. W.: Case of von Recklinghausen's Disease, M. Clin. North America **15**:1267-1273 (March) 1932. Goldstein, I., and Wexler, D.: Spongioneuroblastoma of Optic Nerve in Neurofibromatosis (Recklinghausen), Arch. Ophth. **7**:259-267 (Feb.) 1932. Diaso, F. A.: Elephantiasis Neuromatosis: Case, Urol. & Cutan. Rev. **36**:104-107 (Feb.) 1932. Telford, E. D., and Stapford, J. S. B.: Arterial Thrombosis Associated with Neurofibromatosis of Lumbar Sympathetic Cord, Lancet **2**:16-17 (July 4) 1931. Moore, R. F.: Diffuse Neurofibromatosis with Proptosis, Brit. J. Ophth.

(Footnote continued on next page)

paratively little attempt to weave together the many loose threads of this clinicopathologic syndrome. During the past three years thirty-one patients with Recklinghausen's neurofibromatosis have been observed. In this report it is proposed to demonstrate examples of the multiple manifestations of the condition and to emphasize the influence of various physiologic factors and life experiences on the disease.

ETIOLOGY

Though many theories have been advanced, the cause of Recklinghausen's neurofibromatosis is unknown. The disease is not limited to

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15:272-279 (May) 1931. Phelan, H. V.: Multiple Neurofibromas of Nasociliary Nerve, Arch. Ophth. **5**:800-802 (May) 1931. Anzinger, F. P.: Congenital Plexiform Neurofibromas and Elephantiasis Neuromatosa of the Right Arm and Neck (von Recklinghausen's Disease), J. A. M. A. **96**:1381-1382 (April 25) 1931. Smith, F. R.: Neurofibroma of Ovary Associated with von Recklinghausen's Disease, Am. J. Cancer **15**:859-862 (April) 1931. Beatty, N. M., and Cregor, F. W.: Neurofibromatosis, Familial, with Unusual Manifestations, J. Indiana M. A. **24**:72-76 (Feb.) 1931. Russum, B. C., and Barry, M. W.: Paraganglioma in Suprarenal Medulla with Neurofibromatosis, Nebraska M. J. **15**:243-244 (June) 1930. Goldstein, I., and Wexler, D.: Melanosis Uveae and Melanoma of the Iris in Neurofibromatosis, Arch. Ophth. **3**:288-296 (March) 1930. Callender, G. R., and Thigpen, C. A.: Two Neurofibromas in One Eye, Am. J. Ophth. **13**:121-124 (Feb.) 1930. Sachs, E.: Multiple Neurofibromatosis (von Recklinghausen's Disease) Affecting Posterior Root of Cervical Nerve with Pressure on the Spinal Cord, J. Missouri M. A. **26**:180-192 (April) 1929. Rogers, L.: Macrodactylia in Child Due to Neurofibromatosis (Elephantiasis Neuromatosa), Brit. J. Surg. **16**:684-686 (April) 1929. Pack, G. T.: Unilateral Neurofibromatosis of Cranial and Deep Cervical Nerves: Report of a Case, Arch. Neurol. & Psychiat. **21**:919-923 (April) 1929. Spittal, R. L., and Fernando, S. E.: Elephantiasis Neuromatosa: Case Report, Brit. M. J. **1**:596-597 (March 20) 1929. Hine, M. L., and Wyatt, R. B. H.: Neurofibromatosis of Right Orbit: Case, Brit. J. Ophth. **12**:513-518 (Oct.) 1928. Hoey, T.: Von Recklinghausen's Disease Associated with Fibroma of the Appendix, Brit. M. J. **2**:490 (Sept. 15) 1928. Eller, J. J.: Incomplete Form of von Recklinghausen's Disease: Report of Cases, Arch. Dermat. & Syph. **17**:648-649 (May) 1928. Goodwin, W. H.: Von Recklinghausen's Neurofibromatosis with Report of Cases, Virginia M. Monthly **55**:79-88 (May) 1928. Robinson, J. H.: Neurofibromatosis: Report of Two Cases, Lancet **2**:1074 (Nov. 19) 1927. Bridgeman, M. L.: Von Recklinghausen's Disease, or Neurofibromatosis, Northwest Med. **25**:144-145 (March) 1926. Wiener, A.: Case of Neurofibromatosis with Buphthalmus, Arch. Ophth. **54**:481-488 (Sept.) 1925. Fleming, G. W. T. H., and Cookson, H. A.: Case of Multiple Neurofibromata Associated with True Angioneurofibroma of Acoustic Nerve, Jacksonian Epilepsy and Osteoporosis, J. Neurol. & Psychopath. **6**:104-113 (Aug.) 1925. Shouldice, E.: Neurofibromatosis: Case with One Fibroma Enlargement into Stomach, Canad. M. A. J. **15**:66-69 (Jan.) 1925. Parker, H. L.: A Case of von Recklinghausen's Disease with Involvement of Peripheral Nerves, Optic Nerve and Spinal Cord, J. Nerv. & Ment. Dis. **56**:441-452 (Nov.) 1922. Elliott, C. A., and Beifeld, A. F.: Generalized Neurofibromatosis (von Recklinghausen's Disease): Report of a Case Showing a Superficial Resemblance to Hodgkin's Disease, J. A. M. A. **63**:1358-1362 (Oct. 17) 1914.

the white population but has been reported in the black, red and yellow races also. It is said to be slightly more common among males. In many cases it is almost impossible to determine the age of the patient at the time of the onset of the disease. Though cutaneous pigmentation and tumors may be present at birth, it seems more common for the pigmentation to develop during early infancy, with the insidious appearance of the tumors in later life. As Thomson [2] has pointed out, it is reasonable to assume that the disease has existed long before it can be recognized. This fact is especially true when one considers the distinct hereditary tendency of the disease. Though it was long suspected, it was not until 1915 that Preiser and Davenport [3] in a study of one hundred and fifteen offspring of twenty patients found that 43.5 per cent of the offspring were affected. This at once suggested that the hereditary factor in neurofibromatosis is a dominant one. They found that the disease tends to recur without a break in several generations, with little or no difference in the distribution as regard to the sex of the parent who transmitted the disease. In addition, there seems to be a definite familial resemblance as to the type and location of the principal tumors, the tendency to produce similar pigmentation, the tendency to produce confluent tumors (elephantiasis) and, finally, the tendency for sarcomas to develop. This familial resemblance of the distribution of the tumors is strikingly exemplified in Gardner and Frazier's [4] report of a family in which there were thirty-eight persons with deafness due to bilateral acoustic neurofibromas, fifteen of whom subsequently became blind. Various associated congenital and developmental anomalies, such as cerebral meningocele, spina bifida, cranial defects and defects of the fingers and toes, are found with significant frequency.[5] There are occasional cases in which there is no apparent familial or hereditary history.

Intoxication, infection, mental distress and various external factors, such as exposure to cold, irritation and trauma, have all been suggested as possible causes of the disease. It seems more probable that their influence, if any, is that of stimulation or aggravation.[6] Such a stimu-

2. Thomson, Alexis: On Neuroma and Neurofibromatosis, Edinburgh, Turnbull and Spears, 1900.

3. Preiser, S. A., and Davenport, C. B.: Multiple Neurofibromatosis (von Recklinghausen's Disease) and Its Inheritance, with Description of a Case, Am. J. M. Sc. **156**:507-540 (Oct.) 1918.

4. Gardner, W. J., and Frazier, C. H.: Bilateral Acoustic Neurofibromas, Arch. Neurol. & Psychiat. **23**:266-302 (Feb.) 1930.

5. Knapp, A. A.: Von Recklinghausen's Disease, M. Rec. **139**:62-64 (Jan. 17) 1934.

6. Penfield, W., and Young, A. W.: Nature of von Recklinghausen's Disease and Tumors Associated with It, Arch. Neurol. & Psychiat. **23**:320-344 (Feb.) 1930.

lative action on the course of the disease has been frequently observed in puberty, pregnancy and the menopause.[7]

In attempting to find an explanation of the syndrome known as Recklinghausen's neurofibromatosis, it is only natural that certain observers have turned their attention to a possible endocrinopathy.[8] The multiplicity of the various manifestations, the pigmentation of the skin and the osseous involvement all favor such a relationship. In addition, a number of cases have been reported in which there was associated acromegaly and various other endocrine dysfunction. Furthermore, the detrimental effect on Recklinghausen's neurofibromatosis of such physiologic factors as puberty, menstruation, pregnancy and the menopause seem to point toward an endocrine influence. Though early French and Italian authors endeavored to establish such a connection between Recklinghausen's disease and glandular dysfunction, this hypothesis has only recently been mentioned in the English literature. Levin,[9] in summarizing the different endocrine syndromes that were associated with Recklinghausen's disease before 1921, included menstrual anomalies, incomplete and delayed sexual development, acromegaly, cretinism, myxedema, tetany and Addison's syndrome. He gave as his conclusion that the endocrine system, especially the adrenal glands, play the major rôle in the causation of neurofibromatosis. His review of the necropsy examinations of the involved endocrine glands is interesting and suggestive but is far from conclusive. Tucker,[10] impressed with the endocrine relationship, especially in regard to the pituitary gland, found acromegaloid manifestations in three of nine cases, while in two additional cases a large sella was noted on roentgen examination. Barber and Shaw[11] reported two cases of Recklinghausen's disease associated with pituitary tumors. It is of interest that Marie,[12] in his treatise on acromegaly published in 1891, included cutaneous tumors

7. (*a*) Harbitz, F.: Multiple Neurofibromatosis, Arch. Int. Med. **3**:32-65 (Feb.) 1909. (*b*) Weber, F. Parkes: Periosteal Neurofibromatosis with a Short Consideration of the Whole Subject, Quart. J. Med. **23**:151-155 (Jan.) 1930. (*c*) Noyes, A. W. F.: Histopathology of Molluscum Fibrosum, J. Path. & Bact. **9**:240-245, 1904. (*d*) Ward, E.: Multiple Pigmented Warts in Pregnancy, Brit. J. Dermat. **25**:153-154 (April) 1913. Thomson.[2] Preiser and Davenport.[3]

8. (*a*) Phillips, H. T.: Von Recklinghausen's Disease: Often a Difficult Surgical Problem, South. M. J. **27**:212-215 (March) 1934. (*b*) Goodhart, S. P.: Neurofibromatosis (von Recklinghausen's Disease), in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1923, vol. 10, pp. 665-667.

9. Levin, O. L.: Recklinghausen's Disease: Its Relation to the Endocrine System, Arch. Dermat. & Syph. **4**:303-321 (Sept.) 1921.

10. Tucker, Beverly: Von Recklinghausen's Disease, with Special Reference to the Endocrine System, Arch. Neurol. & Psychiat. **11**:308-320 (March) 1924.

11. Barber, H. W., and Shaw, M.: Brit. J. Dermat. **34**:207-208 (Feb.) 1922.

12. Marie, P., and Suoza-Leite: Essays on Acromegaly, London, Adlard & Son, 1891.

of the face and neck, which he termed molluscum fibrosum, as a part of the characteristic findings of the disease. However, Atkinson [13] in a recent study of seven hundred and sixty-eight reports of cases of acromegaly collected from the literature, found Recklinghausen's disease present in only four cases.

In contradistinction to the endocrine theory of the primary cause of Recklinghausen's neurofibromatosis, Clark and Wakefield [14] suggested the possibility that involvement of the endocrine system is a secondary complication of the disease and that the primary pathologic involvement is sympathetic or parasympathetic or both. Schneiderman [15] and Weber [7b] stated that since all other organs may be involved in the disease, so may the endocrine glands. Gordon [16] had a patient with an acromegaloid appearance who showed a normal sella and pituitary gland, while Gould [17] had the opportunity of studying several cases in which there were changes of the osteomalacic type and observed no postmortem changes in either the pituitary gland or the parathyroid glands. Gordon,[18] in analyzing the literature, stated the conclusion that nothing definite has been advanced to prove that the endocrine glands act in themselves as an etiologic factor but that a common genetic factor is responsible for both sets of symptoms. What little organotherapy has been tried in this disease has had little or no effect on the cutaneous manifestations.[19]

The theory of a congenital embryonal disturbance has often been advanced as a possible explanation of neurofibromatosis. Pende [20] said he believed that two factors are necessary for the production of the disease: (1) a hereditary constitutional factor, represented by an abnormal endocrine-sympathetic system, and (2) an accidental factor, such as shock, trauma, toxic poison or infection, which, through its effect on the endocrine-sympathetic system, acts as a stimulus to the embryonal elements. Schneiderman [15] suggested that there is "a physical, chemical

13. Atkinson, F. R. B.: Acromegaly, London, John Bale, Sons & Danielsson, Ltd., 1932.

14. Clark, G. F., and Wakefield, E. G.: Cardiovascular Disease as a Complication of Generalized Neurofibromatosis, Arch. Dermat. & Syph. **13**:806-814 (June) 1926.

15. Schneiderman, H.: Recklinghausen's Disease, Arch. Dermat. & Syph. **12**: 483-491 (Oct.) 1925.

16. Gordon, S.: Hemorrhage as a Complication of von Recklinghausen's Disease, Canad. M. A. J. **27**:524-525 (Nov.) 1932.

17. Gould, E. P.: Bone Changes Occurring in von Recklinghausen's Disease, Quart. J. Med. **11**:221-227 (April) 1918.

18. Gordon, M. B.: Endocrine Consideration: Report of a Case with Associated Childhood Myxedema, Endocrinology **13**:553-563 (Nov.-Dec.) 1929.

19. Gordon.[18] Levin.[9] Knapp.[5]

20. Pende, cited by Levin.[9] Muto, A.: Riv. di pat. nerv. **15**:656-670, 1910.

or nutritional disturbance in the environment of the developing embryo at the stage when the ectoderm is forming the nervous system" and that this defect is "transmitted to the following generations according to the mendelian law." Ewing [21] expressed the belief that the underlying factor is a disturbance in the relations between the fetal ectoderm and the tissues which it innervates, while Miller [22] supported the hypothesis that neurofibromatosis is a manifestation of a congenital disturbance of the mesenchyme. Yakovlev and Guthrie [23] and more recently Schwarz and Abramson [24] agreed that the disease is probably due to a congenital maldevelopment of organs of ectodermal derivation but added to neurofibromatosis both tuberous sclerosis and angiomatosis of the brain, with nevi of the skin in the trigeminal area, as additional overlapping and parallel congenital malformations. These they classed as congenital ectodermoses (neurocutaneous syndromes).

CLINICAL TYPES

There is considerable difficulty in attempting to define and differentiate the various clinical types of Recklinghausen's neurofibromatosis. With such widespread lesions affecting almost any part of the body and more especially the skin and nervous system, no two cases are similar. The term neurofibromatosis is misleading in that it lays undue emphasis on only one part of the clinical manifestations, viz., the cutaneous and subcutaneous tumors. Though this is a common part of the syndrome, it is usually present in the cases of more advanced and complete involvement. Pigmentation of the skin, osseous changes and elephantiasic thickenings of soft tissues, alone or in combination, also are to be considered characteristic features of the disease. The term Recklinghausen's disease has been suggested as a more inclusive term than neurofibromatosis.

Incomplete Form.—The irregular patches of yellowish brown, café au lait pigmentation may be the only manifestation of the disease.[25]

21. Ewing, James: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922, pp. 152-154.

22. Miller, Alexander: Neurofibromatosis with Reference to Skeletal Changes, Compression, Myelitis and Malignant Degeneration, Arch. Surg. **32**:109-122 (Jan.) 1936.

23. Yakovlev, P. I., and Guthrie, R. H.: Congenital Ectodermoses (Neurocutaneous Syndromes) in Epileptic Patients, Arch. Neurol. & Psychiat. **26**:1145-1194 (Dec.) 1931.

24. Schwarz, H., and Abramson, H.: Neurocutaneous Syndromes in Childhood, J. Pediat. **3**:586-607 (Oct.) 1933.

25. (*a*) Leader, S. D., and Grand, M. J. H.: Von Recklinghausen's Disease in Children: Report of a Case Presenting Cutaneous Pigmentation and Bone

This monosymptomatic form, the so-called incomplete type, or forme fruste, is usually found in a child with a parent or some other relative who has the complete form of the disease. The pigmentation is thought to be due to fibromatosis of the terminal filaments of the cutaneous nerves.[22] The pigmentation, which is usually confined to the trunk and unexposed surfaces, may precede by years the formation and appearance of the characteristic cutaneous and subcutaneous nodules. It is rarely symmetrical and does not follow the distribution of any particular nerve or nerves.[2] The spots and patches of pigmentation usually increase in number and size with advancing years. Pigmentation is said to be present in only 25 per cent of the cases,[26] but from our experience and from a survey of the literature it seems that it is present in a much higher percentage of cases.

Neurofibromatosis.—The general character of the cutaneous and subcutaneous tumors of Recklinghausen's disease are too well known to need further description. Their variability in location, distribution and size is well appreciated. They may occur in the skin or subcutaneous tissues, the deep or superficial nerves, the sympathetic or parasympathetic nerves or the cranial or spinal nerves. They may be small or large, localized or diffuse, single or multiple. Although they are usually painless, they may cause pain through pressure on or involvement of the nerve roots. The size and number of the tumors may be progressive or may remain stationary. The growths rarely regress in size. They are most commonly found on the trunk and are usually associated with cutaneous pigmentation. When the lesions are confined to the skin the condition is termed molluscum fibrosum, but Weber[7b] warned that the presence of one or two small tumors is not at all rare in an otherwise normal subject. If the neurofibroma is confined to the distribution of one or more contiguous nerves or a plexus of nerves, the term plexiform neurofibroma has been applied.

Osseous Changes.—At first considered an accidental association, skeletal deformity has now come to be regarded as an important and characteristic part of Recklinghausen's disease.[27] This is not to be

Changes, J. Pediat. **1**:754-763 (Dec.) 1933. (*b*) Wise, F., and Eller, J. J.: Von Recklinghausen's Disease Without Tumor Formation: Incomplete or Abortive Forms of the Disease, J. A. M. A. **86**:86-90 (Jan. 9) 1926. (*c*) Weber, F. Parkes: Cutaneous Pigmentation as an Incomplete Form of von Recklinghausen's Disease, with Remarks on the Classification of Incomplete and Anomalous Forms of von Recklinghausen's Disease, Brit. J. Dermat. **21**:49-53 (Jan.) 1909. Goodhart.[8b]

26. Thomson.[2] Harbitz.[7a] Knapp.[5]

27. Stewart, C. C.: Neurofibromatosis in Children: Report of Two Cases, New England J. Med. **210**:150-152 (Jan. 18) 1934. Copeland, M. M.; Craver, L. F., and Reese, A. B.: Neurofibromatosis with Ocular Changes and Involvement of the Thoracic Spine, Arch. Surg. **29**:108-112 (July) 1934. Miller.[22]

confused with Recklinghausen's hyperparathyroidism. In 1921 Weiss [28] called attention to the presence of scoliosis in fifteen cases of neurofibromatosis, but it remained for Brooks and Lehman [29] to describe and classify the various types of osseous changes present in their seven cases. These included (1) scoliosis, by far the most common, (2) abnormalities of growth, most commonly associated with elephantiasis, and (3) subperiosteal cysts. All the osseous changes have been explained by involvement of the bone by growth of the tumor. The deformity may be noted first in early childhood. Weber [7b] has recently substantiated this explanation. Gould [17] mentioned a fourth type of osseous change in describing findings similar to osteomalacia. Lehman [30] in a later paper again stressed the osseous changes as being of great diagnostic importance and added the cystic areas in the skull, detected only by complete roentgenographic examination. Pigmentation of the skin and osseous changes may occur in the absence of palpable or visible neurofibromatosis.[31] Twenty-three per cent of all the tumors of the spinal cord are neurofibromas, and a competent roentgenologist can directly localize the lesion in 42 per cent of the cases through alterations in the structure of the vertebrae and adjoining ribs and soft tissues.[32] Erosion of vertebral bone with compression myelitis has occurred.[22] It is emphasized that a complete roentgenographic examination should be made in all cases of Recklinghausen's disease.

Elephantiasis Neuromatosa.—This form of Recklinghausen's neurofibromatosis usually occurs as a part of the more advanced stage of the disease and in general consists of a prominent diffuse overgrowth of the skin and subcutaneous tissue of the head, neck, trunk or extremity. More than one third of the elephantiasic overgrowths originate in the temporal region. They are more common in men [33] and are nearly always unilateral.[7b] They may result, either singly or in combination with general cutaneous manifestations, from a large molluscum fibrosum

28. Weiss, R. S.: Von Recklinghausen's Disease in the Negro: Curvature of Spine in von Recklinghausen's Disease, Arch. Dermat. & Syph. **3**:144-151 (Feb.) 1921.

29. Brooks, B., and Lehman, E. P.: Bone Changes in von Recklinghausen's Neurofibromatosis, Surg., Gynec. & Obst. **38**:587-595 (May) 1924.

30. Lehman, E. P.: Recklinghausen's Neurofibromatosis and the Skeleton: A Plea for Complete Study of the Disease, Arch. Dermat. & Syph. **14**:178-187 (Aug.) 1926.

31. Schwarz and Abramson.[24] Leader and Grand.[25a]

32. Camy, J. D.: A Roentgenologic Study of Osseous Changes with Neurofibromatosis of the Spinal Cord and Associated Nerves, Proc. Staff Meet., Mayo Clin. **8**:329-341 (April 19) 1933.

33. Helmholz, H. F., and Cushing, Harvey: Elephantiasis Nervorum: A Manifestation of von Recklinghausen's Disease, Am. J. M. Sc. **132**:355-378 (Sept.) 1906.

or from a plexiform neurofibroma.[2] The tumor is often unsightly and horribly disfiguring and with an increase in size becomes pedunculated or pendulous. The tumor may be either a lobular or a diffuse overgrowth. The overlying skin is usually pigmented and may be either smooth or, more commonly, hard and uneven.

In addition to these four loosely knit and overlapping types of Recklinghausen's disease, there are other clinical manifestations that have been reported in the literature with such significant regularity that they too must be included as a minor part of the symptom complex.

Deafness.—Neuroma of the acoustic nerve is most commonly single and constitutes 7.3 per cent of all verified tumors of the brain.[34] A high percentage of the more rare bilateral tumors of the acoustic nerve are associated with Recklinghausen's disease.[35] They originate in the vestibular portion of the eighth nerve. In 1930 Gardner and Frazier [4] found that a total of thirty-seven cases had been reported in which such a tumor was associated with neurofibromatosis and seven others in which it was apparently unassociated with other evidence of the disease. The deafness may begin on one side, the usual age at onset varying from 20 to 35 years. Progressive bilateral nerve deafness, progressive recession of vision, with choked disk, and other late signs of increasing intracranial pressure are the usual procession of events unless an early diagnosis is made and neurosurgical intervention is carried out.

Mental Defect.—Imbecility, mental aberration and psychic disturbances are integral parts of the complete picture of the disease.[36] Leader and Grand [25a] stated as their opinion that it is a result of an endocrine influence and that mental deficiency is not a common finding. However, Charpentier [37] found that 63 per cent of his patients showed mild psychic defects, with a tendency to depression. Preiser and Davenport [8] found that 7.8 per cent of two hundred and forty-three patients were feebleminded (twenty times more than in the average population). Yakovlev and Guthrie [23] gave as their opinion that congenital anomalies of the skin are relatively more common among epileptic patients than among persons with other illnesses or among normal persons.

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34. Cushing, Harvey: Tumors of the Nervus Acusticus, Philadelphia, W. B. Saunders Company, 1917, pp. 148 and 210.

35. (*a*) Symonds, C. D.: Bilateral Eighth Nerve Tumors Associated with Multiple Neurofibromatosis, J. Neurol. & Psychopath. **2**:143-153 (Aug.) 1921. (*b*) Jacobsen, V. C.: Fibroma of the Acoustic Nerve, Am. J. Path. **1**:259-272 (May) 1927.

36. Gordon.[18] Yakovlev and Guthrie.[23]

37. Charpentier, quoted by Bassoe, P., and Nuzum, F.: Report of a Case of Central and Peripheral Neurofibromatosis, J. Nerv. & Ment. Dis. **42**:785-796 (Dec.) 1915.

PATHOLOGIC PICTURE

Since von Recklinghausen [38] originally described the tumors as originating in the connective tissue (1882), controversy has centered about their development from mesodermal or ectodermal tissue.[35b] The result has been the use of such terms as multiple neuroma, peripheral glioma, schwannoma, perineurial fibroblastoma and multiple neurinoma in the pathologic description.

In Virchow's [39] description the tumors of this disorder were classed as false neuromas because of the lack of nerve cells. Thomson [2] in his description subdivided Virchow's classification into solitary and multiple false neuromas. In more recent years the tumors of the nerve sheaths have been said by Verocay,[40] Masson [41] and others to arise from cells of the sheath of Schwann and to be ectodermal in origin. Penfield,[42] on the basis of his own exhaustive studies and the work of Mallory,[43] Rhoads and Van Wagenen,[44] stated the belief that the tumors of the nerve sheath are due to a reaction of the connective tissue. Because the outstanding histologic characteristics are suggestive of such a reaction, he referred to the solitary tumor of the nerve sheath of the same type as a perineurial fibroblastoma and retained the common term for the multiple tumors—the neurofibroma of Recklinghausen's disease. Penfield [42a] has stated that the two types of tumor may be differentiated. The presence of nerve fibers in the tumors show that one is dealing with a neurofibroma and not a perineurial fibroblastoma. In the latter the nerve fibers of the parent nerve will be found about the tumor in the capsule, not entering the tumor.

Histologically the neurofibromas of Recklinghausen show considerable variation. There is no typical pattern, as is the case in fibro-

38. von Recklinghausen, F.: Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen, Festschrift, Rudolf Virchow, Berlin, A. Hirschwald, 1882.

39. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863, p. 3.

40. Verocay, J.: Zur Kenntnis der "Neurofibrome," Beitr. z. path. Anat. u. z. allg. Path. **48**:1, 1910.

41. Masson, P.: Recklinghausen's Neurofibromatosis, Sensory Neuromas and Motor Neuromas, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, pp. 793-802.

42. Penfield, Wilder: (*a*) Tumors of the Sheaths of the Nervous System, Arch. Neurol. & Psychiat. **27**:1298-1309 (June) 1932; (*b*) Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, sect. 19. Penfield and Young.[6]

43. Mallory, F. B.: The Type of Cell of the So-Called Dural Endothelioma, J. M. Research **41**:349, 1920.

44. Rhoads, C. P., and Van Wagenen, W. P.: Observations on the Histology of the Tumors of the Nervus Acusticus, Am. J. Path. **4**:145-152, 1928.

blastomas, but rather a bizarre intermixture of the tumor fibers. Occasionally areas are seen where there is a palisade arrangement, with the nuclei in long rows, a characteristic feature of the perineurial fibroblastoma. Penfield [42b] remarked that the appearance of perineurial fibroblastic growth within the tumor is doubtless due to some type of irritation of the perineurial connective tissue.

The variation in the pathologic picture has been remarkable in isolated cases. Kernohan and Parker [45] reported a most striking case of neurofibromatosis in which postmortem examination showed associated multiple meningioma and perineurial fibroblastoma. The meningeal tumors showed all stages of activity from those almost entirely made of psammoma bodies to those with hyperchromatic and giant nuclei as well as mitotic figures. A somewhat similar case with associated gliomas has been reported by Penfield [42a] and Young.

Another interesting chapter in the pathology of Recklinghausen's disease is that of sarcomatous change or malignant transformation. The literature on this subject has been covered by Hosoi [46] in his report of two cases of multiple neurofibromatosis in which malignant transformation developed. He stated the belief that this sarcomatous development bears further evidence of the mesodermal origin of the neurofibroma. In a résumé Hosoi stated that malignant transformation takes place in about 13 per cent of all cases of Recklinghausen's disease. With the development of sarcomatous changes there is metastasis in 22 per cent. It is rare for malignant changes to develop in more than two isolated tumors, although recently Miller [22] described a case in which malignant degeneration of varying degree was present in almost all the seven larger tumors studied. He expressed the belief that the sarcomatous degeneration took place simultaneously in the several neurofibromas rather than that the changes were metastatic.

PROGNOSIS AND TREATMENT

Harbitz [7a] stated: "The patients die with the disease and not from it." Extensive neurofibromatosis may be unattended by any symptoms, and unless there is visible or palpable evidence of the disease, it may remain unsuspected and unrecognized until discovered at postmortem examination. From the standpoint of clinical evolution, Schuhman and Terris discriminated: (1) a stationary form, (2) a subacute form, with exacerbations and remissions of the growth of tumors, (3) an acute form, with a rapid and striking development of generalized neurofibromatosis, and (4) a malignant form, with sarcomatous degeneration of the tumors and metastasis. Though for the most part the disease

45. Kernohan and Parker, cited by Mallory.[43]

46. Hosoi, cited by Rhoads and Van Wagenen.[44]

may be harmless, with advancing years various serious complications may occur and alter the otherwise innocent course of the disease. It should be especially emphasized that the prognosis of an "incomplete" form of the disease in a young subject presenting only pigmentation should be carefully guarded. There may be such complications as cosmetic unsightliness; involvement of the central nervous system, with resultant deafness, pain and mental deficiency; development of growth abnormalities and skeletal deformities resulting from osseous involvement; bizarre secondary endocrine manifestations, or, finally, ulceration, hemorrhage, infection or malignant degeneration of tumor growths. In a middle-aged woman repeated pregnancies may stimulate the growth of the cutaneous manifestations to a marked degree and thereby enhance a predisposition to serious complications.[47] Even for adult patients the prognosis should be guarded, as it has been found that in 72 per cent of the cases of malignant degeneration of benign neurofibroma to sarcoma the disease begins in the third, fourth or fifth, decade.[44] It is of interest to note that hemorrhage, spontaneous, following slight injury or occurring during the surgical removal of a tumor has been reported as a complication in several instances.[48] It seems to concern especially the large, elephantiasic types of tumor.[49]

No beneficial treatment of Recklinghausen's disease has been found. Women with the "incomplete" form of the disease should be warned about the detrimental effect of pregnancy and the dominant mendelian hereditary tendency passed on to offspring.[47] As mentioned, organotherapy is practically useless. The tumors are not affected by roentgen or radium therapy. Surgical excision may be resorted to if the tumors become too large, cause pain or interfere with activity. Phillips,[50] however, warned that these patients are poor surgical risks, as they are particularly susceptible to shock and profuse hemorrhage. If surgical excision of a tumor is to be performed, it should be complete, as partial removal of a neurofibroma predisposes to malignant degeneration.[44] In some cases malignant transformation occurs after a single operation. In other cases, even after repeated operations, no malignant

47. Sharpe, J. C., and Young, R. H.: Neurofibromatosis: The Effect of Pregnancy on the Skin Manifestations, J. A. M. A. **106**:682-683 (Feb. 29) 1936.

48. Carrington, G. L., and Bullitt, J. B.: Hemorrhage in a Case of von Recklinghausen's Disease, J. A. M. A. **87**:166-167 (July 17) 1926. Gordon.[16] Knapp.[5]

49. Heurer, G. T., and Bell, H. G.: Hemorrhage and Infection of Large Tumors (Pachydermatoceles) of von Recklinghausen's Disease, Ann. Surg. **94**: 15-24 (July) 1931.

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changes arise. After surgical excision recurrence of the tumor growth may be frequent; it is generally local or regional but may be followed by crops of multiple neurofibromas elsewhere.

REPORT OF CASES

CASE 1.—H. W. was a boy aged 15. His father, his grandfather, one aunt and one cousin had cutaneous manifestations of the disease. The patient's skin was

Fig. 1.—Neurofibromatosis, case 1.

clear at birth. He began to walk at 1½ years of age, but two years later a decided limp developed. Brownish pigmentation of the skin appeared when he was 7. The different diseases of childhood had no effect on the pigmentation. Progressive enlargement of the left leg, noted during childhood, increased markedly after he was 13. During the past two years there had been an increasing number of areas of pigmentation. He had not been aware that any subcutaneous nodules were present until he was examined and a dozen small tumors were felt beneath the skin of the enlarged left leg. Roentgenograms of the affected extremity showed a marked growth deformity of the bones, but no subperiosteal neurofibromas could be demonstrated (fig. 1).

CASE 2.—A. W. was a man aged 45, father of H. W. (case 1). His father, sister and son showed cutaneous manifestations of the disease. His skin was clear at birth, but during infancy café au lait spots of pigmentation appeared. A few nodules appeared on the skin of the back during puberty but had not increased in the last twenty years.

CASE 3.—M. J. was a woman aged 42. Her three sisters and three daughters had the disease. The entire trunk, arms and thighs were covered with irregular areas of brownish pigmentation with cutaneous and subcutaneous tumors of various sizes. Her skin had been clear at birth, but pigmentation appeared shortly afterward and persisted during the various diseases of childhood, puberty and four pregnancies. The cutaneous tumors first appeared with the fifth pregnancy and increased with each of two successive pregnancies. She had had partial unilateral deafness for six years. Her three youngest children had the "incomplete" form of the disease.

CASE 4.—E. J. was a girl aged 8, daughter of M. J. (case 3). Her mother and two younger sisters had cutaneous manifestations. The pigmentation of the skin of the neck and body first appeared when she was 3. The usual diseases of childhood had no stimulative effect, and there were no palpable tumors.

CASE 5.—J. J. was a girl aged 6, daughter of M. J. (case 3). Her mother and two sisters had the disease. Pigmentation of the body was noted shortly after birth and had increased slightly thereafter. No palpable tumors were present.

CASE 6.—K. J. was a girl aged 4, daughter of M. J. (case 3). Her mother and two sisters had the disease. One or two rather large café au lait spots of pigmentation appeared on the back during her first year of life.

CASE 7.—B. C. was a woman aged 31 (fig. 2). There was no family history of the disease. When first pregnant, when 19, she noted the appearance of pigmentation and many soft pedunculated tumors over the trunk. During two miscarriages and one other pregnancy there has been a definite increase in all the cutaneous manifestations. One large painful tumor was removed from the breast, and during the operation there was profuse bleeding. The physician made a diagnosis of "nerve tumor." The two living children had no cutaneous manifestations of the disease.

CASE 8.—D. W. was a girl aged 10. There was no family history of the disease. The skin was clear at birth, but when she was 3 years old a mass appeared in the left cheek and slowly increased to the size of an egg. Palpation revealed several discrete painless tumors in the distribution of the left facial nerve. After she was 5 years old several other tumors appeared in the skin of the trunk and scalp, accompanied with several small areas of brownish pigmentation on the back. A biopsy showed the tumor of the cheek to be a neurofibroma. The patient was definitely mentally retarded and was two years behind children of her age at school.

CASE 9.—M. E. was a woman aged 38 (fig. 3). Her mother, maternal grandfather and two children had evidence of the disease. She had had a few spots of pigmentation since childhood. There seemed to be no stimulative effect from the usual diseases of childhood, an attack of pneumonia or puberty. Since shortly after she learned to walk there had been progressive curvature of the spine. Her first two pregnancies had no influence on the skin, but with each of the next four pregnancies cutaneous tumors appeared, with increased pigmentation. There had been one miscarriage. Her two youngest children, aged 10 and 3 years, had the "incomplete" form of the disease.

CASE 10.—J. E. was a girl aged 10, daughter of M. E. (case 9). Her mother, her grandmother and a sister had the disease. Since the age of 2 years the patient had had a few spots of pigmentation on her arms and back, and for the past three years she had been aware of a mass in her right cheek which had steadily become larger.

CASE 11.—G. E. was a girl aged 3, daughter of M. E. (case 9). Her mother, her grandmother and a sister had the disease. There were several rather large areas of pigmentation of the skin on the back and upper part of the arms that had

Fig. 2.—Neurofibromatosis, case 7.

appeared first after birth. There had been no recent change in the pigmentation or any sign of tumor formation.

CASE 12.—E. C. was a woman aged 56. Her father and one daughter had the disease. Except for a few so-called freckles over the trunk, the patient's skin was clear before her marriage. Accompanying her first and each of seven successive pregnancies, there appeared multiple cutaneous tumors, with an increase in pigmentation. Moderate scoliosis developed. She had been bedridden for one year because of pain in the left sciatic nerve. One adult daughter had the complete form of the disease, and one son was heavily pigmented over the body.

Case 13.—N. C. was a woman aged 24, daughter of G. E. (case 11). Her mother and grandfather had the disease. Since she was a small child the patient had had multiple patches of pigmentation of the trunk. When she was 9 years old a small cutaneous tumor developed at the base of the neck, and during puberty several more such tumors appeared. Though married, she had not been pregnant.

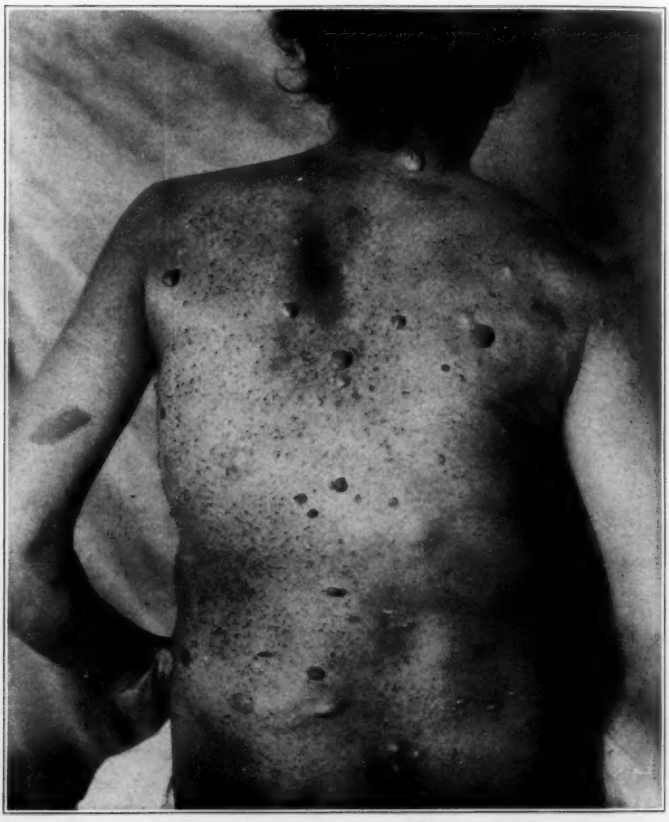

Fig. 3.—Neurofibromatosis, case 9.

Case 14.—J. A. was a woman aged 34. Her mother, her brother and one son had the disease. The skin had been perfectly clear until her first pregnancy, when she noted the sudden appearance of cutaneous pigmentation and tumor growth. Following delivery there was a cessation of growth, which did not flare up with her second pregnancy. A tumor in the cervical intervertebral foramina resulted in constant pain and scoliosis (fig. 4). There was a nontoxic adenoma of the thyroid gland. One of her two sons had the "incomplete" form of the disease.

CASE 15.—F. A. was a boy aged 7, son of J. A. (case 14). His mother and grandmother had the disease. The patient presented one large area of brown pigmentation on the upper portion of one arm and several areas on the back. The pigmentation had come on soon after birth, with no appreciable increase in the past few years (fig. 5).

CASE 16.—S. G. was a man aged 21. There was no family history of the disease. At birth there were a few areas of light brown pigmentation distributed over the trunk. During puberty there was a definite increase in the amount of

Fig. 4.—Tumor of the cervical intervertebral foramina, case 14.

pigmentation, and multiple cutaneous tumors appeared. There had been no recent change in the skin.

CASE 17.—G. H. was a woman aged 62. Three brothers, one sister and one daughter had the disease. Her skin was clear when she was a child and up to the time of her marriage. Though not certain, she believed that the cutaneous pigmentation and the multiple cutaneous and subcutaneous tumors occurred with her first pregnancy and increased with each of four successive pregnancies. There was a definite increase in all the cutaneous manifestations during the menopause.

CASE 18.—F. C. was a woman aged 23, daughter of G. H. (case 17). Her mother, one aunt and three uncles had the disease. Since infancy she had had a number of pigmented areas over her trunk. During childhood multiple cutaneous

tumors appeared over the head, neck and body. The cutaneous changes increased with puberty and again during her first pregnancy, when she was 22. Her baby's skin was clear at birth. The patient presented also unilateral progressive deafness.

CASE 19.—E. M. was a woman aged 66, sister of G. H. (case 17). One sister, three brothers and one son had the disease. Her skin was clear in childhood and until after her marriage. With the first and each of seven successive pregnancies multiple cutaneous and subcutaneous tumors appeared about the head and neck. The menopause had no effect on the cutaneous signs.

CASE 20.—F. M. was a man aged 25, son of E. M. (case 19). His mother, an aunt and three uncles had the disease. The skin had been clear until six years previously, when a single large painless tumor suddenly appeared beneath the skin of the left forearm. The trunk showed a large area of pigmentation, which had come on at approximately the same time.

Fig. 5.—Neurofibromatosis, case 15.

CASE 21.—S. H. was a man aged 64, brother of G. H. and E. M. (cases 17 and 19). Two sisters and two brothers had the disease. The patient believed he had a few cutaneous tumors at birth, with no increase until the age of puberty, when he became literally covered with the irregular-sized nodules, even over the scalp and palms. A moderate degree of scoliosis was present. Surprisingly enough, there has been little or no change in the size or number of tumors for fifty years (fig. 6).

CASE 22.—J. H. was a man aged 61, brother of S. H. (case 21). Two sisters and two brothers had the disease. Multiple cutaneous tumors had appeared on both arms and a few on the trunk "years ago," with no known change for "a long time."

CASE 23.—A. H., a woman aged 24, knew of no family history of the disease. Her skin had been clear until puberty, when generalized small cutaneous and subcutaneous tumors and café au lait pigmentation appeared. A large plexiform

neurofibroma formed in the left cheek and encroached on the external auditory canal so that hearing was impaired. This tumor was partially removed, a biopsy disclosing that it was a "neurofibroma." In addition, a nontoxic adenoma of the thyroid gland was removed. Though the patient had experienced three pregnancies, the last was the only one to cause any noticeable increase in the size and number

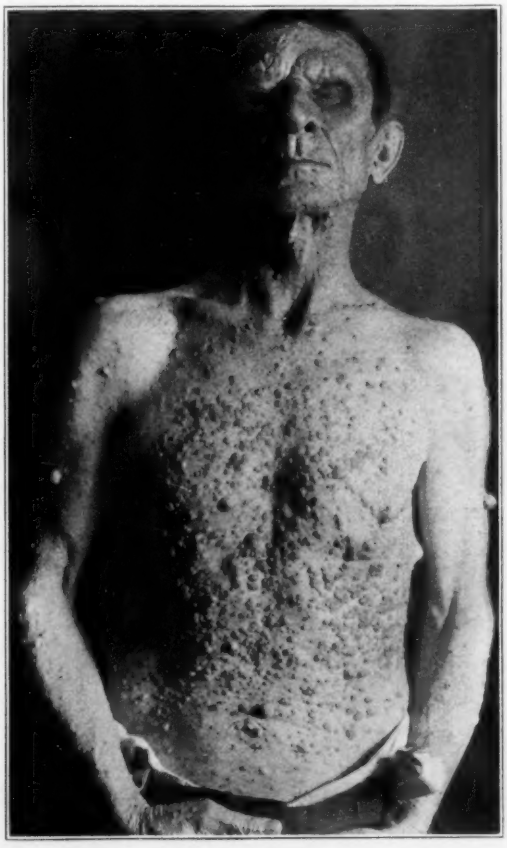

Fig. 6.—Generalized neurofibromatosis, case 21.

of the cutaneous tumors. None of this patient's children had any evidence of the disease.

CASE 24.—F. S., a woman aged 22, knew of no family history of the disease. There had been no evidence of the disease until after an attack of scarlet fever when she was 19, at which time there was a sudden occurrence of generalized neurofibromatosis, with the formation of a large plexiform neurofibroma on the

left side of the face (fig. 7). Partial deafness resulted from this overgrowth of tissue. Later the growth was removed.

CASE 25.—B. F. was a woman aged 22. One sister and a son had the disease. The patient's skin was clear at birth, but pigmentation appeared during infancy. After "malarial fever" when she was 9, a few cutaneous tumors appeared on the body. Puberty apparently had no appreciable effect on the disease. With each of three pregnancies there was a definite increase in all the cutaneous manifestations. Her oldest boy, aged 4 years, had the "incomplete" form of the disease.

CASE 26.—G. F. was a boy aged 4, son of B. F. (case 25). His mother and aunt had the disease. Several large areas of pigmentation were first noted when he was 1 year old. No palpable tumor was present.

Fig. 7.—Neurofibromatosis, case 24.

CASE 27.—G. O., a man aged 36, knew of no family history of the disease. Curvature of the spine was first noted when he was 3, and at about the same time two or three irregular areas of brownish pigmentation were apparent on the trunk. During puberty a large painless mass appeared below the angle of the right jaw. No new tumor had appeared in the last twenty years.

CASE 28.—B. R. was a woman aged 28. Her father had the disease. Multiple areas of cutaneous pigmentation had been noted since infancy. Also during this time beginning scoliosis was noted, which became extreme with advancing years. Numerous diseases of childhood had no apparent effect, but the onset of menstruation at the age of 19 caused the appearance of a few cutaneous tumors. With each of two pregnancies, both ending in miscarriage, there was a marked increase in the number of tumors until the trunk was almost covered.

CASE 29.—F. R. was a man aged 52, father of B. R. (case 28). He had a doubtful family history of the disease, although his daughter had advanced

neurofibromatosis. His skin was clear when he was a child, but after the age of 14 a large deforming tumor of the gluteal region and several small tumors about the face and neck developed. No new tumors or increase in the size of the present tumors had been noted for the past twenty-five years.

CASE 30.—C. C., a single woman aged 33, knew of no family history of the disease. The skin was clear at birth, but when she was 2 years old a tumor of the eye appeared. When she was 3 the eye was enucleated. Multiple cutaneous tumors appeared when she was 12, and increased in number during a pregnancy when she was 31. When 33 she had a tumor about the orbit operated on, but the operation was unsuccessful because of excessive hemorrhage. After each of three

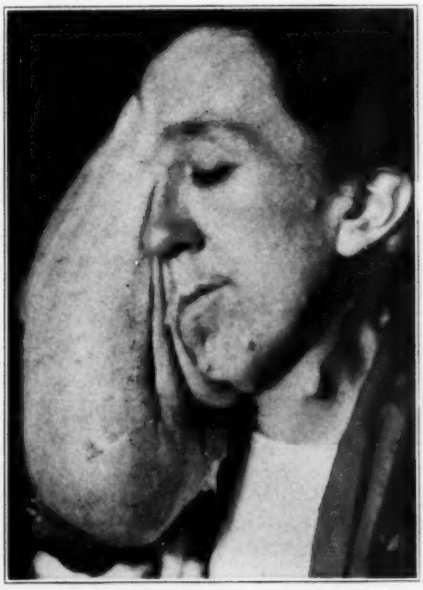

Fig. 8.—Tumor about the orbit, case 30

operations there was growth of the mass (fig. 8). The tumor was finally successfully removed by electrocautery. Subsequently sarcomatous (?) metastasis to the lungs developed, and two years later the patient died. No autopsy was made.

CASE 31.—F. W., a farmer aged 26, knew of no family history of the disease. Tumors of the feet were first noticed when he was 11, and as they became enlarged there was local pain over a period of six years. There were three attempts at operative removal of the painful tumors. Since the first appearance there has been a steady growth of the tumors and an increase in their number. From the time of the first appearance of a tumor about two years passed before it would become painful. The neural status was normal.

COMMENT

Though this paper presents one of the largest series of cases reported, the number is too small to allow any definite conclusive statements relative to the etiology, the occurrence of different clinical types and the possible complications of the disease. However, our figures seem to be in close harmony with those for the larger groups of case reports collected from the literature and should at least serve as a fair guide in a clinical study. Of our thirty-one patients, eleven were males and twenty females. The ages varied from 3 to 66 years. A family history of the disease was obtained in 74 per cent of the cases. The changes in the skin, nerves and bones are summarized in table 1. For the most part, both pigmentation and cutaneous tumors were present at the time of our examination, although seven patients, all less than

TABLE 1.—*Types of Clinical Cases*

	Number of Cases
Pigmentation alone	7
Pigmentation and tumors	24
Tumors:	
Generalized	17
Plexiform	7
Osseous changes:	
Vertebral	6
Long bones	1
Elephantiasis	2
Complications:	
Deafness	5
Mental disorder	1
Pain	4
Hemorrhage	3
Malignant growth	1

10 years of age, presented only the "incomplete" pigmentary changes. In all the cases of our series various degrees of pigmentation were noted. The tumors were most commonly generalized, distributed over the trunk and extremities, but seven patients showed the large localized type of plexiform neurofibromas. Evidence of intracranial involvement was suggested in two cases of progressive unilateral deafness, whereas in three other cases deafness was due to encroachment on the external auditory canal by a large plexiform neurofibroma of the face. There were two cases of mental retardation. As a result of tumor growth, pain was the presenting feature in four cases. Osseous changes were noted in seven patients, six having a moderate or severe degree of scoliosis and the remaining patient presenting an osseous deformity of the lower extremity associated with elephantiasic overgrowth of tissue. Elephantiasis nervorum also was present to an extreme degree in one other case. Other associated congenital abnormalities were conspicuously absent.

On inspection of the reports with regard to the type of clinical manifestations which were present during the different age groups, it is of interest and importance that the youngest patients showed only pigmentation of the skin, while the older patients showed cutaneous and subcutaneous tumors and, subsequently, the more serious osseous and elephantiasic changes (table 2). On critical analysis of the histories with respect to the age of the patient at the time of onset and the possible factors influencing exacerbations of the disease, it is significant that in the majority of cases pigmentation began in early infancy and increased during puberty and pregnancy (table 3). In a few cases the

TABLE 2.—*Types of the Disease at Different Ages*

Age, Years	Number of Cases	Pigmentation	Tumors		Osseous Changes	Elephantiasis
			General	Local		
1-10	8	8	1	2	..	..
11-20	1	1	1	..	1	1
21-30	8	8	7	3	1	..
31-40	5	5	4	1	3	1
41-50	2	2	2	..	..	..
51-60	3	3	2	1	..	..
61-70	4	4	4	..	..	..

TABLE 3.—*Clinical Types of the Disease at Different Periods of Life*

	Pigmentation		Tumors		Osseous Changes	
	Onset	Exacerbation	Onset	Exacerbation	Onset	Exacerbation
Birth	2	..	1	..	..	..
Infancy	16	..	1	..	4	..
Childhood	1	2	3	1	..	1
Diseases	1	1	2	..	..	..
Puberty	4	4	7	4	1	1
Pregnancy	5	8	7	8	2	1
Menopause	..	1	..	1	..	..

clinical appearance of tumors was noted during infancy and childhood, but most commonly the tumors became evident during puberty and during pregnancy. In most of our cases the osseous changes began during infancy. In two cases diseases of childhood and the later more serious illnesses apparently had some slight stimulative effect on the course of the disease. Occupation, environment and mental stress had no definite connection with the clinical signs. The surgical removal of small tumors for biopsy and of the larger ones either for the relief of pain or for the cosmetic effect was not followed by any unusual growth phenomena. However, one patient who was operated on subsequently showed malignant degeneration and died of metastatic sarcoma. Severe operative hemorrhage occurred in three cases.

Because of the endocrine theory of the etiology of this disease, a survey of the series for related endocrinopathy was made. Though

menstrual irregularities were fairly frequent and the incidence of miscarriages seemingly was large, no adequate explanation could be found to account for them. The menopause was apparently associated with an increase in the cutaneous changes in one case. Pregnancy occurred fifty times among eleven women, and thirty-six of these pregnancies (72 per cent) caused either the onset or an exacerbation of the disease (table 4). With the exception of three patients, all women in whom a nontoxic adenoma of the thyroid gland was discovered, no other endocrine dysfunction was noted. In addition to a careful history and physical examination in all cases, a more complete study of the endocrine system was possible in six cases. The height, weight, blood pressure, roentgenograms of the bones and sella turcica, basal metabolic rate, dextrose tolerance and calcium and phosphorus content of the blood were studied. In every instance they were found to be within normal

TABLE 4.—*Effect of Pregnancy*

	Hereditary	Congenital
Married women	9	2
Number of pregnancies	43	7
Number of miscarriages	9	3
Pregnancies causing onset of exacerbation	32	4
Number of children of such pregnancies	30	4
Number of children with clinical signs	11	0
Number of children without clinical signs	19	4
Pregnancies not causing onset of exacerbation	6	2
Number of children of such pregnancies	4	0
Number of children with clinical signs	0	0
Number of children without clinical signs	4	0

limits. Except for the pigmentation of the skin, we have not been impressed with any clinical similarity between Recklinghausen's disease and Addison's syndrome. We have observed two patients with acromegaly, both of whom had numerous skin tags, sebaceous cysts and soft fibromas about the head and neck and who might have been accidentally included in this series had not biopsy of the skin been made. One case of myxedema in which there were similar cutaneous changes also was excluded.

One of the most outstanding features in the study of our cases was the progressive, changeable course of the disease with the advance of years. The characteristic nosologic concept of this disease has been a static picture of a variety of pathologic changes in the skin, nerves and bones, but our experience has led us to formulate a dynamic presentation of the disorder which stresses the influence of various life experiences and physiologic factors on the natural history of the disease, including such factors as heredity, birth, infancy, childhood, adolescence and pregnancy. The clinical manifestations of the disease during midlife

present a vastly different picture from those during childhood when there may be only a few café au lait spots of pigmentation on the back. As previously pointed out, the wide variations of clinical types in Recklinghausen's disease is well recognized, but that a varying progression of the disease may occur in the subject as a result of the influence of different physiologic factors has not been sufficiently emphasized. The progressive changes in the clinical course may be exemplified by the following hypothetic case. At the age of 3 years a child is brought to a pediatrician because of multiple areas of cutaneous pigmentation; at the age of 7 she is taken to an orthopedist because of beginning scoliosis; at 15 she may notice the appearance of a few soft, painless, cutaneous and subcutaneous tumors and may seek the advice of a dermatologist, and during the early twenties she may ask her obstetrician why the pigmentation and cutaneous tumors become more numerous and prominent during pregnancy. At the age of 30 she may be referred to an otologist, who makes a diagnosis of progressive nerve deafness and sends her to a neurosurgeon for removal of the bilateral tumors of the acoustic nerve. A few years later, because of constant pain in the left thigh, she may consult a neurologist, who will find involvement of the sciatic nerve. Later, an internist may advise surgical removal of a large pendulous tumor of the breast, which has undergone malignant degeneration. Thus, the patient reaches the pathologist's postmortem table. At any time during the entire life of such a patient some specialist might give a diagnosis of neurofibromatosis without truly appreciating the complete evolution of the disease.

The question naturally arises: What common factor or factors are present during the different age periods that cause such steplike exacerbations and so influence the course of the disease? From a study of our patients we suggest that from an etiologic standpoint a division of the patients into two groups is possible: (1) patients without any family history of the disease, who, at least in our experience, do not pass the disease on to their offspring—patients with the so-called congenital type —and (2) the larger group of patients who show a family history of the disease and who tend to pass the inheritance on to their children—patients with the so-called inherited type. The affected offspring of patients with the inherited type of disease may or may not present evidence of the disease at birth, but a latent tissue abnormality is present nevertheless. On the other hand, in patients without a family history of the disease, it is conceivable that for some unknown reason there is a congenital maldevelopment of some mesodermal tissue in utero which may be clinically manifest at birth or may lie as a dormant embryonic arrest for a number of years. Whether the condition is inherited or congenital in origin, its potential

possibilities are the same. Its embryonic character is subject to the stimulation of growth activity through infancy, childhood and puberty, just as all other normal tissue is influenced during these periods. If the clinical signs are present at birth, they may continue to increase during the first two decades of life, or, if absent, they may become apparent for the first time during this period. In our group of men and nonpregnant women between 20 and 25 years of age, few new tumors were noted, and in some instances there seemed to be a cessation of the growth of the nodules. In the occasional case after this age, the older and larger tumors continue to grow slowly. It seems possible, therefore, that two factors may be necessary for the production of this disease: (1) primary maldevelopment of mesodermal tissue, which may be either inherited or congenital in origin, and (2) a secondary quantitative response of this abnormal tissue to the normal physiologic growth stimulus that is supplied during the first two decades of life.

If this hypothesis is correct, how can one explain the exacerbations of the disease during pregnancy? It might be reasonable to suppose that in any case of Recklinghausen's disease of either the inherited or the congenital type the latent embryonic arrests in the mother are powerfully stimulated by the growing fetal tissue and that a clinical flare-up of the disease is noted. This exacerbation of the cutaneous manifestations may not occur during the first or even the second pregnancy but may be noted during the third or fourth pregnancy. It appears, however, that once an exacerbation occurs during pregnancy, with each succeeding pregnancy there will be a similar response. Emge [51] stated as his conclusion that "neoplastic tissue sensitive to hormonal stimuli may exhibit increased activity during pregnancy," and though a dermoid cyst ordinarily does not enlarge with pregnancy, a cystic teratoma may, at times, enlarge rapidly. He pointed out further the well known fact that a benign adenoma of the breast responds to the stimulus of pregnancy in the same ratio as does normal mammary tissue and that the activating factor must necessarily be hormonal in origin. It is not surprising, therefore, that carcinoma of the breast is unfavorably influenced by pregnancy. One interesting and perhaps significant fact revealed by our series is that pregnancy caused an exacerbation in the cutaneous manifestations in approximately 72 per cent of the cases of inherited Recklinghausen's disease and that in over one third of the children of these particular pregnancies the disease has developed. As the children grow older we expect more of them to show clinical manifestations of involvement. On the other hand, when the pregnancy did not cause the onset or an exacerbation, we have not yet noted develop-

51. Emge, L. A.: Influence of Pregnancy on Tumor Growth, Am. J. Obst. & Gynec. **28**:682-697 (Nov.) 1934.

ment of the disease in the offspring. It is also pertinent to point out that none of the children of parents who carry the congenital type of disease show any clinical evidence of pigmentation or tumor growth.

That pregnancy may influence the course of Recklinghausen's disease is of considerable importance in considering the prognosis and treatment. Each additional pregnancy adds to the possibility of exacerbation and spread of the various tumor growths, which, in turn, may lead to more serious complications, such as involvement of the central nervous system, osseous changes, disfigurement or malignant degeneration. The chances of such complications are higher with the advance of years and repeated pregnancies, so that the prognosis for young persons should be guarded. After experiencing alarming changes in the skin several of our patients have requested sterilization. Observing the same telltale brownish pigmentation of the skin in their children that they themselves once had, they have insisted that no further pregnancies be permitted. If any part of neurofibromatosis can be prevented, it seems that pregnancy offers the main hope of control. In cases of inherited neurofibromatosis the disease is usually made worse by pregnancy, and there is a 50 per cent chance that the disease will develop in the offspring. In the case of males with a family history of the disease the same holds true for their offspring. Though pregnancy will cause an exacerbation of the disease in a woman with the congenital type of neurofibromatosis, the disease does not and theoretically should not develop in the children.

SUMMARY

A review of the literature on Recklinghausen's disease reveals a variety of etiologic factors, a tendency to classify the features of the disease into clinical types, the controversy as to whether the tumors are mesodermal or ectodermal in origin and the utter lack of any successful treatment.

A study of our thirty-one cases of Recklinghausen's disease fails to reveal any new clinical features or remarkable combinations of previously described manifestations. However, from this study certain conclusions have emerged. It is suggested that from a congenital or inherited mesodermal abnormality an embryonic tissue arrest is formed, which at birth or during infancy, childhood, puberty or pregnancy may become clinically manifest, depending on its response to the stimulation of the normal physiologic growth factor. This reaction to the influence of physiologic factors and life experiences leads to the progressive and changeable course of the disease. The clinical features that any particular patient may present will be dependent on his age, the congenital factors and his individual sensitivity to stimulating influences.

Of all the influences studied in the thirty-one cases, pregnancy produced the most stimulative effect in the progressive course of the disease. This effect has been mentioned in the past, but its dramatic nature has not been fully appreciated. In this disease, which is in a large percentage of cases hereditary and which is without beneficial treatment, it seems that avoidance of pregnancy affords the chief opportunity for control and arrest.

It is hoped that further attention to the history of the disease during the life of affected subjects, rather than a consideration of the more classic, static, nosologic cross-section of the disease that the patients present at any life period, will be productive of a more helpful management.

CONCLUSIONS

A review of thirty-one cases of Recklinghausen's disease has been presented with reference to the clinical manifestations at different life periods.

Recklinghausen's disease is caused by a reaction of mesodermal tissue that presents a variable picture, with changes over a period of years resulting from the influence of various life experiences and physiologic growth factors.

Pregnancy is the most potent factor in stimulating the progressive course of the disease. The avoidance of pregnancy seems to offer the greatest opportunity for the arrest of the progressive course and control of the disease.

Drs. H. F. Tyler, C. C. Tomlinson, O. J. Cameron, J. M. Christlieb and J. R. Redgwick permitted us to examine their patients.

ABSTRACT OF DISCUSSION

Dr. W. M. Ketcham, Kansas City, Mo.: Neurofibromas are simple tumors which occur in connection with superficial or deep nerves. They grow from the perineurium and endoneurium and as they increase in size the nerve fibers become expanded over or buried in them. The tumors may be rounded and either hard or soft and are frequently multiple. Function is not necessarily affected by them.

Neurofibromas are divided into two groups—central and peripheral. Central neurofibromas occur commonly within the skull, particularly in relation to the root of the eighth nerve, and are known as neurofibromas of the acoustic nerve. The fibromas of the skin and deep tissues of the limbs are of this type. The tumors arise from the motor and sensory nerves rather than from the sympathetic fibers.

The authors suggest the etiologic classification—congenital and hereditary tumors.

Cutaneous neurofibromas may be single or multiple. The condition known as neurofibromatosis, molluscum fibrosum or Recklinghausen's disease is characterized by multiple neurofibromas, with localized distribution to single nerve trunks or to the whole body.

Larger tumors frequently have pedicles and become pendulous. Thickening and pigmentation of the overlying skin develop, and occasionally there is softening or maldevelopment of the bones. Cerebral tumors are rare. Slowly progressive but essentially benign, the tumors may be removed without recurrence.

The authors show that the physiologic epochs of infancy, childhood and especially adolescence and pregnancy exert a great influence in changing the characteristics of this disease. Pregnancy is the greatest factor. Neurofibromatosis, however, is present in men also, so that if there is an endocrine growth-stimulating factor, it must be one factor or a combination of factors peculiar to both sexes. As a rule, pregnancy increases the basal metabolic rate from 10 to 20 per cent plus, so that normal readings indicate a relative deficiency. During pregnancy the cellular activity is increased and may definitely influence the frequent activation and growth of neurofibromas. Theoretically there should be an increase in the secretion of the eosinophilic cells of the anterior pituitary gland during pregnancy, so as to account for the remarkable stimulation to the tissue of the growing fetus. I suggest trying combinations of thyroid, solution of adrenal cortex and a preparation of the anterior lobe of the pituitary gland containing the growth-stimulating hormone if there are any evident changes after a year's observation. The most important hormone should be the growth-stimulating principle inherent in the anterior lobe of the pituitary gland, because the periods of the greatest growth of neurofibromas are during adolescence and pregnancy.

Dr. J. J. Eller, New York: Most dermatologists feel that this disease is hereditary, even though at times it is difficult to bring out in the history that a parent or grandparent showed signs of the disease. I have reported on a few cases in which certain members of a family had distinct and well developed neurofibromatosis and other members in the third or fourth decade of life showed only slight but typical pigmentation of Recklinghausen's disease, in other words, abortive forms.

This particular type of the disease is of interest to physicians for the following reasons: Some of these patients appear with vague muscular or osseous pains or some aural disturbance of vague etiology or even an ocular disturbance. Perhaps, with further study, it would be found that there was a family history of Recklinghausen's disease of the abortive type.

No local destruction that I know of—and my colleagues and I have experimented with various types of removal by surgical measures and coagulation—in any way affects the tumors. They always recur. No glandular therapy that is known today has in any way affected the course of this condition. I agree with Drs. Sharpe and Young that sterilization is the one hope, in order to prevent not only exacerbations of the disease in women but also the bringing forth of children who would suffer from this serious malady.

Regarding the mental changes about which so much is said in the literature, I consider that mental aberration is a rarity rather than the rule.

Dr. Richard H. Young, Omaha: Dr. Ketcham brought out the fact that there was also the cranial type of neurofibromatosis. In discussing that point it is well to mention that the ordinary tumor of the eighth nerve is a solitary tumor and of a different type histologically. It has been called by Penfield a perineurial fibroblastoma. Of course, neurofibroma of the eighth nerve does occur in this disease.

In reference to the effect of pregnancy, it was of interest to us that in our male patients we saw practically no exacerbation or increase in the size or in the number of the tumors after the period of adolescence.

I wish to emphasize the fact that we have been chiefly interested in the natural history of this disease and the dynamic factor that influences the course. We have been interested also in the clinical types or cross-section view of the disorder as it appears at the different periods of life. The chief exciting factors seem to be the physiologic changes of infancy, puberty and pregnancy, and of these, pregnancy has been the least appreciated and yet, in our series, provoked the most dramatic changes.

In this disease, for which there is no specific treatment, it seems to us the avoidance of the possible stimulating factors offers the chief opportunity for control.

Progress in Internal Medicine

DISEASES OF METABOLISM AND NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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I. DISEASES OF METABOLISM

By DR. WILDER

DIABETES MELLITUS

Protamine Insulin.—The discovery of Hagedorn [1] that protamines will combine loosely with insulin, giving flocculant precipitates that are relatively insoluble in the fluids of the tissues, whereby prolonged hypoglycemic effects are obtained, has received much attention during this past year. All the American and Canadian manufacturers of insulin, cooperating with the Insulin Committee of Toronto, have undertaken the manufacture of such preparations. A large number of clinicians have been supplied with material for trial, and several thousand patients have already received treatment with the new compounds.

The reports of clinicians that have appeared are those of Hagedorn,[1] Krarup,[2] Root,[3] Lawrence,[4] Leyton,[5] Kerr,[6] Sprague,[7] Rabinowitch,[8]

From the Division of Medicine, the Mayo Clinic.

The section on "Nutrition" will be published in the March issue of this journal.

1. Hagedorn, H. C.; Jensen, B. Norman; Krarup, N. B., and Wodstrup, I.: Protamine Insulinate, J. A. M. A. **106**:177-180 (Jan. 18) 1936.

2. Krarup, N. B.: Clinical Investigations into the Action of Protamine-Insulin, Copenhagen, G. E. C. Gad, 1935.

3. Root, H. F.; White, Priscilla; Marble, Alexander, and Stotz, E. H.: Clinical Experience with Protamine Insulinate, J. A. M. A. **106**:180-183 (Jan. 18) 1936.

4. Lawrence, R. D., and Archer, Nora: Some Experiments with Protamine Insulinate, Brit. M. J. **1**:747-749 (April 11) 1936.

5. Leyton, O.: Protamine Insulinate, Brit. M. J. **1**:443 (Feb. 29) 1936.

6. Kerr, R. B.; Best, C. H.; Campbell, W. R., and Fletcher, A. A.: Protamine Insulin, Canad. M. A. J. **34**:400-401 (April) 1936.

(Footnotes continued on next page)

Winnett,[9] Joslin,[10] Black,[11] Bowcock,[12] Smith[13] and Allen[14] and the associates of these workers. The verdict on the whole is highly favorable and almost unanimous. Fewer injections and, in most cases, a smaller number of units are required to maintain a satisfactory level of sugar in the blood. The reactions are fewer and less severe, and the general health of the patient frequently is improved. These are important advantages. However, apprehension is expressed by many that widespread use of the new preparation, involving as it does a technic which differs in important particulars from that required for giving regular insulin, will result in many serious accidents. It is highly important, therefore, that physicians acquaint themselves with what now has been published about protamine insulin before prescribing it.

As originally distributed, protamine insulin was supplied in two vials, one containing 4 cc. of U 50 water-soluble insulin, the other 1 cc. of a suitably buffered solution of protamine. The directions stated that the contents of the two vials were to be combined shortly before using. The resulting precipitate was stable only for a limited number of days. Later, it was found that the addition of traces of zinc, 0.2 mg. per hundred units of insulin, imparts stability to the precipitate and, therefore, recently the material for distribution has been supplied already mixed in one vial. Hereafter in this paper, unless otherwise stated, protamine insulin with zinc added in this proportion will be meant whenever the term protamine insulin is employed. It is expected that

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7. Sprague, R. G.; Blum, B. B.; Osterberg, A. E.; Kepler, E. J., and Wilder, R. M.: Clinical Observations with Insulin Protamine Compounds, J. A. M. A. **106**:1701-1705 (May 16) 1936. Wilder, R. M.: The New Insulin, Minnesota Med. **20**:6-15 (Jan.) 1937.

8. (*a*) Rabinowitch, I. M.; Fowler, A. F., and Corcoran, A. C.: Observations on the Action of Protamine and Insulin in the Treatment of Diabetes Mellitus, Canad. M. A. J. **35**:124-129 (Aug.) 1936. (*b*) Rabinowitch, I. M.; Foster, J. S.; Fowler, A. F., and Corcoran, A. C.: Clinical Experiences with Protamine-Zinc-Insulin and Other Mixtures of Zinc and Insulin in Diabetes Mellitus, ibid. **35**:239-252 (Sept.) 1936.

9. Winnett, E. B.: The Treatment of Diabetes with Protamine Insulin, J. Iowa M. Soc. **26**:231-237 (May) 1936.

10. Joslin, E. P.; Root, H. F.; Marble, Alexander; White, Priscilla; Joslin, A. P., and Lynch, G. W.: (*a*) Protamine Insulin, New England J. Med. **214**: 1079-1085 (May 28); (*b*) Protamine Insulin, Tr. A. Am. Physicians **51**:174-187, 1936.

11. Black, D. R.: Protamine Insulin, J. Missouri M. A. **33**:212-215 (June) 1936.

12. Bowcock, Harold: Observations on the Treatment of Diabetes with Protamine Insulin in Office and Hospital, South. M. J. **29**:701-704 (July) 1936.

13. Smith, B.: Clinical Studies with Protamine-Insulin, California & West. Med. **45**:144-148 (Aug.) 1936.

14. Allen, F. M.: Some Difficulties Arising in the Use of Protamine Insulinate, J. A. M. A. **107**:430-431 (Aug. 8) 1936.

the product will be placed on the market shortly after Jan. 1, 1937, and that the cost to the patient will not exceed that of treatment with regular insulin.

Some objection was raised to the addition of zinc, and for a time calcium was used. It improved the stability of the precipitate but not so satisfactorily as zinc; it failed also to prolong the time of action and for these reasons was abandoned. As a matter of fact, fear of the long-continued use of zinc in such minute doses is unjustified. Zinc commonly is present in the pancreas in considerable amount, and insulin always has contained traces of zinc (from 0.05 or less to 0.1 mg. or more per thousand units). Rabinowitch [8b] and his associates have attended to this question. They have pointed out that zinc does not accumulate in the blood of workers who for years have been exposed to its fumes and, furthermore, that zinc has been added to the rations of animals (rats) observed through three generations without producing deleterious effects of any kind.

Duration of Action: The length of time during which an effect can be maintained by a single injection of protamine insulin seems to be much greater in man than in animals. It is commonly supposed that this is accounted for by the larger size of the dose given. The duration of the action is influenced by the size of the dose and by the amount of sugar to be metabolized. The injection of a number of units inadequate for maintenance may reveal little evidence of any prolongation of action (Lawrence and Archer [4]), and even a maintenance dose will act for a shorter time when given with food than when food is withheld. The following studies are cited in illustration:

A patient with severe diabetes was fed at two hour intervals with a mixture of milk, cream and syrup, each feeding representing one twelfth of what previously had been the daily allowance of carbohydrate, protein and fat. Under these circumstances the activity of a large dose (132 units) of protamine insulin containing calcium (1 mg. per hundred units) was exhausted by the end of twenty-four hours. The sugar content by that time had reached the original value, and sugar was appearing in the urine. At the end of twenty-eight hours acetone was present in the urine, and the balance for nitrogen had become negative. At the end of thirty-six hours the carbohydrate-combining power of the plasma had fallen to 32.4 volumes per cent, and the patient exhibited the signs and symptoms of diabetic acidosis (fig. 1). There thus was no reason to believe that the insulin injected was acting after thirty-six hours.

A second patient with diabetes as severe as this was given 70 units of plain protamine insulin and thereafter no food for fifty-seven hours.[15] The sugar value

15. The subject of the first study had not received protamine insulin previously and had been taking daily 88 units of regular insulin in four divided doses. For reasons which will be given later it was assumed that not more than two thirds of the protamine insulin administered would come into play within the first twenty-four hours; therefore, the dose was made to equal 1.5 times 88, or 132 units. The subject of the second study had been maintained in equilibrium beforehand with 70 units of plain protamine insulin a day.

fell gradually to the hypoglycemic level and remained there until the fifty-seventh hour, when feeding was resumed. The patient exhibited no symptoms of hypoglycemia until the end of the period, and clearly the insulin was continuing to act fifty-seven hours after injection (fig. 2).

Added zinc prolongs the activity of insulin and protamine insulin. The duration of activity of the protamine insulin used in the first of the two studies just cited, when compared with another observation

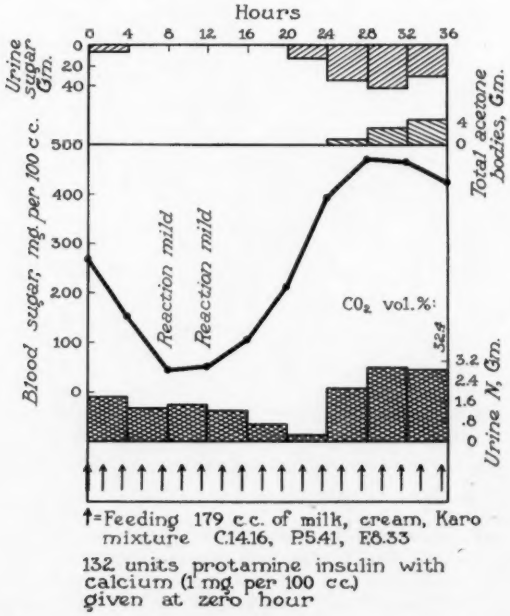
Hours
0 4 8 12 16 20 24 28 32 36
Urine sugar Gm.
0 20 40
Total acetone bodies, Gm.
4 0
Blood sugar, mg. per 100 c.c.
500 400 300 200 100 0
Reaction mild
Reaction mild
CO2 vol.%:
32.4
Urine N, Gm.
3.2 2.4 1.6 .8 0
↑=Feeding 179 c.c. of milk, cream, Karo mixture C.14.16, P.5.41, F.8.33
132 units protamine insulin with calcium (1 mg. per 100 c.c.) given at zero hour

Fig. 1.—The duration of action of protamine insulin containing calcium in a woman aged 32 who was receiving food at two hour intervals.

made of the same patient, illustrates effectively the further prolongation of action imparted to protamine insulin by the addition of zinc:

After the first patient had been given only regular insulin for three days, another study was carried out using protamine insulin containing 2 mg. of calcium per hundred units. The result was the same; if anything the duration of activity was even a little shorter. Then for three days, only regular insulin was used, and the effect of administering 132 units of protamine insulin containing 0.2 mg. of zinc per hundred units was observed. This time, after thirty-six hours the patient remained free from acidosis and was only beginning to excrete sugar (fig. 3).

Why the addition of zinc thus should prolong the action of protamine insulin has not been explained other than by the assumption that

it behaves as a catalyst. Not only zinc but cobalt and nickel occur in the pancreas in appreciable quantities, as has been demonstrated by Fisher and Scott,[16] and various authors have attributed significance to the presence of these ions of heavy metals. Thus, Bertrand and Mâcheboeuf [17] noted that small amounts of cobalt and nickel administered with insulin would increase the quantity of sugar utilized; Maxwell and Bischoff [18] reported that the addition of basic ferric chloride had a similar effect, and Kylin [19] found that potassium ions increased the sugar content of the blood and depressed the action of insulin, whereas calcium ions had the opposite effect. Fazekas and Himwich [20] have

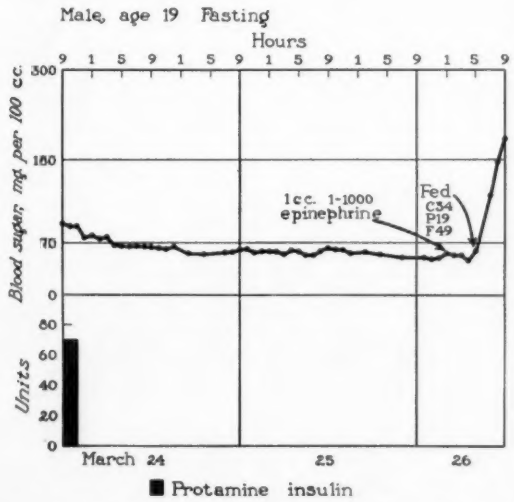

Fig. 2.—The duration of action of protamine insulin during fasting in a man aged 19.

reported that salts of aluminum retard the action of insulin. The amount of zinc in the pancreas is greater than that of these other metals, and zinc has a greater effect on the activity of insulin than either cobalt or potassium. Its action when added to regular insulin, according to

16. Fisher, A. M., and Scott, D. A.: Zinc Content of Bovine Pancreas, Biochem. J. **29**:1055-1058, 1935.

17. Bertrand and Mâcheboeuf, quoted by Scott and Fisher.[21]

18. Maxwell and Bischoff, quoted by Scott and Fisher.[21]

19. Kyling, quoted by Scott and Fisher.[21]

20. Fazekas, J. F., and Himwich, H. E.: The Effect of Zinc and Aluminum on the Hypoglycemic Action of Insulin, J. Pharmacol. & Exper. Therap. **58**:260-263 (Nov.) 1936.

Scott and Fisher,[21] is to extend considerably the period of hypoglycemia (fig. 4). Kerr and his associates [22] called attention to a difficulty that every one treating diabetes seems to have encountered of late; namely, that many more diabetic patients than formerly require more frequent injections of regular insulin. They explained this on the basis of the greater purity of the insulin available in recent years and by the fact that the manufacturers, in securing this greater purity, have diminished

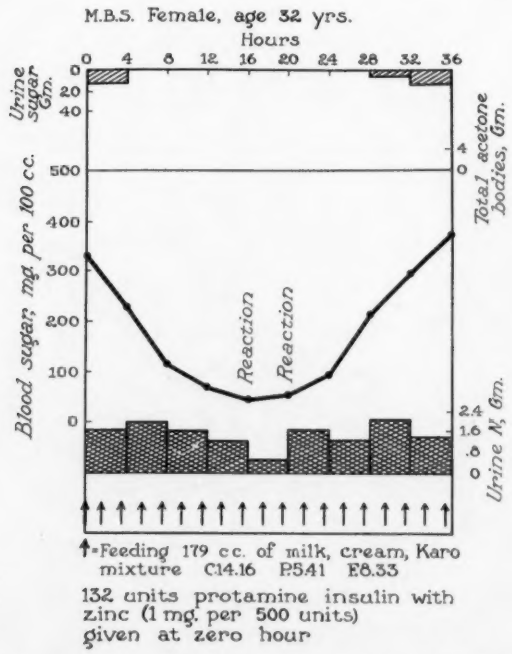

Fig. 3.—The duration of action of protamine insulin containing zinc in a woman aged 32 who was receiving food at two hour intervals.

the previously higher content of metallic salts, principally that of zinc. This, I think, must be the case, because recently, by using regular insulin to which zinc has been added, I have found it possible to maintain several patients with two injections a day who previously required four injections of commercial insulin.

21. Scott, D. A., and Fisher, A. M.: The Effect of Zinc Salts on the Action of Insulin, J. Pharmacol. & Exper. Therap. **55**:206-221 (Oct.) 1935.

22. Kerr, R. B.; Best, C. H.; Campbell, W. R., and Fletcher, A. A.: Protamine Insulin, Canad. Pub. Health J. **27**:157-159 (April) 1936.

Crystalline Insulin: Sahyun [23] crystallized insulin and found that a solution of it had an action that was considerably prolonged as compared with that of commercial insulin. His preparation contained zinc. The presence of traces of zinc or other heavy metals is necessary, indeed, to effect crystallization of insulin, as had been shown before by Scott.[24] But whether or not the longer activity of Sahyun's crystalline insulin is attributable to the zinc is unsettled; Sahyun has said not. The material he prepared for distribution to a few clinicians for trial contained only 0.9 mg. of zinc per thousand units, and by recrystallization he was able to reduce this content to as little as 0.2 or 0.3 mg. per thousand units without loss of prolonged activity. Such minute amounts of zinc will not prolong the action of regular insulin when added to it; indeed, they are smaller than the amounts formerly contained in com-

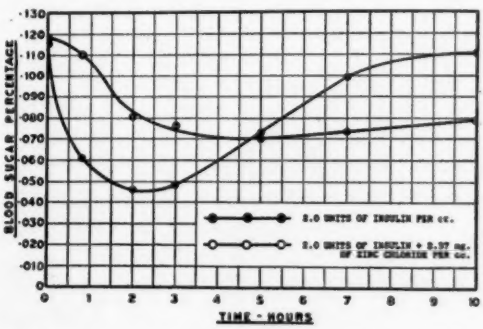

Fig. 4.—The effect of added zinc on the duration of action of regular insulin (from Scott and Fisher).

mercial insulin. Sahyun therefore stated that he supposed that his preparation must owe its prolonged action either to some peculiar chemical reaction between the zinc and the insulin or to some racemization within the large molecule of insulin. On the other hand, spectroscopic analysis of samples of Sahyun's preparation made by Foster revealed a zinc content of from 0.437 to 1.15 mg. per five hundred units, and little difference was found between the action of these samples and crystalline insulin which was prepared by the usual method in the Connaught Laboratories. The duration of action of Sahyun's preparation is such that satisfactory control of hyperglycemia can be obtained in most cases with no more than two injections a day; it is not enough to effect control with only one injection a day, as is illustrated in figure 5.

23. Sahyun, M.: Personal communication to the authors.
24. Scott, D. A.: Crystalline Insulin, Biochem. J. **28**:1592-1602, 1934.

Experience at the Mayo Clinic with this preparation is not greatly different from that reported by Altshuler and Leiser,[25] who found that the duration of action of crystalline insulin does not exceed thirteen or fourteen hours but that the use of this preparation permits better control with fewer doses and fewer total units than is possible with ordinary insulin. Freund and Adler [26] apparently did not take the fullest advantage of the long action of protamine insulin and gave no less than two injections a day. For this reason crystalline insulin in their experience did not appear at a disadvantage.

Another report by Mains and McMullen [27] is more difficult to interpret. Apparently they were dealing with cases of milder diabetes.

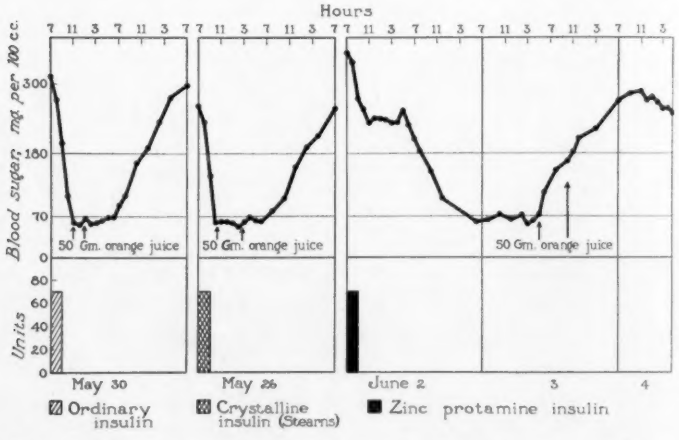

Fig. 5.—A comparative study of the action on the sugar content of the blood of a fasting diabetic man aged 19 of regular insulin, Stearn's crystalline insulin (Sahyun) and zinc protamine insulin. For more than three days before each observation the patient was given 70 units of regular insulin daily in divided doses and a diet containing 150 Gm. of carbohydrate. The evidence from this and similar studies indicates that crystalline insulin acts for little more than twelve hours.

Many of their patients suffered from arteriosclerotic complications, this being a type of diabetes in which not infrequently large overdoses

25. Altshuler, S. S., and Leiser, Rudolph: Clinical Experience with an Improved Crystalline Insulin, J. A. M. A. **107**:1626-1629 (Nov. 14) 1936.

26. Freund, H. A., and Adler, Sidney: Effects of Standard, Protamine and Crystalline Insulin on Blood Sugar Levels, J. A. M. A. **107**:573-577 (Aug. 22) 1936.

27. Mains, M. P., and McMullen, C. J.: The Clinical Investigation of an Improved Crystalline Insulin: Preliminary Report, J. A. M. A. **107**:959-962 (Sept. 19) 1936.

of insulin can be tolerated without symptoms of reactions. Under these circumstances it appeared to these authors that the sugar level of the blood could be satisfactorily maintained with one injection a day of crystalline insulin. Rabinowitch and his colleagues also found in some cases that the prolongation of action of crystalline insulin equaled that of plain protamine insulin, although it was never as great as that of protamine zinc insulin. Their data suggest that the prolongation of action of crystalline insulin is due to its content of zinc. They obtained equally good, and in some cases better, results by the simple addition of zinc to regular insulin and found that large amounts of zinc, enough, for example, to provide a 0.4 per cent concentration, led to actual inhibition of the action of the insulin in 1 case and to great retardation of action in others.

Other insulins with a prolonged action have been originated. One is insulin tannate, which is prepared by Bischoff. It was studied clinically by Gray.[28] A suitable solution of tannic acid is added to regular insulin of U 100 strength, so that the resulting mixture contains 3 mg. of tannic acid per hundred units. The addition must be made immediately before injection. Erythema and subcutaneous swellings occasionally were encountered. These are disadvantages. Another preparation is that of Klein and Grosse.[29] Their "Insulin-Durant" consists of a viscous mixture of lipoids which requires special syringes and needles for injection. Leyton [30] in London in 1929 and Bernhardt and Strauch [31] in Berlin in 1926 also attempted to retard the action of insulin, resorting to mixing it with oil. Bernhardt and Strauch really were the pioneers in this endeavor to prolong the action of insulin.

Methods of Administering Protamine Insulin: Hagedorn, Jensen, Krarup and Wodstrup,[1] who were the first to report on the clinical use of protamine, gave in most cases an injection of protamine insulin in the evening and one of regular insulin in the morning. Root, White, Marble and Stotz [2] at first either followed that schedule or gave two injections a day of protamine insulin. Sprague and his associates,[32]

28. Gray, P. A.: The Treatment of Diabetes Mellitus with Insoluble Insulin Compounds, Endocrinology **20**:461-472 (July) 1936.

29. Klein, G., and Grosse, A.: Theoretische und praktische Ergebnisse mit parenteralen Depots, Ztschr. f. d. ges. exper. Med. **98**:623-650, 1936. Katsch, G.; Scholderer, H., and Klatt, K.: Depotinsulin, Ztschr. f. klin. Med. **129**:608-626, 1936.

30. Leyton, O.: The Administration of Insulin in Suspension, Lancet **1**:756-759 (April 13) 1929; Clin. Med. & Surg. **36**:299-302 (May) 1929.

31. Bernhardt, Hermann, and Strauch, C. B.: Ueber parenteral Depots wasserlöslicher Medikamente, Ztschr. f. klin. Med. **104**:744-766, 1926.

32. Sprague, Blum, Osterberg, Kepler and Wilder.[7] Wilder, R. M.: Clinical Investigations with Insulin Protamine Compound, Proc. Staff Meet., Mayo Clin. **11**:257-258 (April 22) 1936.

impressed by the evidence that the full effect of an injection of protamine insulin was not exhausted until some time after the first twenty-four hours, were led to treat patients with one injection, giving the entire dose for the day in the morning before breakfast. This procedure was adopted also by Campbell [33] and later by Joslin [10b] and Rabinowitch [8b] and their associates and by others. It usually is satisfactory, although in cases of severe diabetes a supplementary dose of regular insulin is required to prevent glycosuria after meals. There is no reason to fear the relatively large size of the single dose if the injection is made in the morning, because before the peak effect is obtained the patient has received both breakfast and the noon meal, and these prevent excessive lowering of the sugar content of the blood. The principal difficulty at present with the single morning injection is that the Insulin Committee in Toronto has consented thus far to the distribution of protamine insulin only in the U 40 strength. Their explanation is that the duration of action is affected by the volume of the injected material, but in consequence of being limited to material of this strength patients requiring more than 40 units for the day must either use a larger volume of material than is pleasant or divide the dose and make two simultaneous injections. It is to be hoped that protamine insulin of U 80 strength will be found to be equally effective.

An advantage of giving all the insulin for the day in a single injection and making this injection before breakfast is that by this technic the qualitative test of the morning urine for sugar becomes an accurate guide to dosage. Tests at other times of the day reflect the hyperglycemic effect of meals, and such postprandial hyperglycemia and glycosuria may occur even when the dose of protamine insulin is so large that it will provoke a reaction at night. When the entire dose is given before breakfast, the morning test, if positive, shows that the dose is inadequate and can be increased with safety. If negative, it indicates that the dose is as much as can be tolerated, and any evidence of a reaction then becomes an indication for a smaller dose.

Diets with Protamine Insulin: Campbell,[33] Joslin [10b] and Sprague [7] and their colleagues have expressed the opinion that greater latitude in the amounts of foods may be allowed to patients using protamine insulin. Good results have been obtained with diets high in carbohydrate by Rabinowitch and with diets high in fat and low in carbohydrate by Campbell. On the whole, according to Campbell's experience, patients receiving diets moderately low in carbohydrate have lent themselves more readily to treatment with a single large dose than patients on other types of diet.

33. Campbell, W. R.; Fletcher, A. A., and Kerr, R. B.: Protamine Insulin in the Treatment of Diabetes Mellitus, Tr. A. Am. Physicians **51**:161-173, 1936.

Economy Effected with Protamine Insulin: With protamine insulin, especially that to which zinc has been added, the average patient requires a smaller number of units a day. The average saving has been about 25 per cent, but in occasional cases the saving may be much greater. Rabinowitch and his colleagues attributed this need for less insulin to an increased sensitivity to insulin imparted by the zinc, but as yet the evidence for this is not entirely satisfactory. The facts suggest that insulin is protected by zinc or bound to the cell for a longer period, instead of being rushed past the liver and other tissues, perhaps to be excreted. It is as if the zinc acted like a hook or, to use Ehrlich's metaphor, like a side chain. The saving effected is not at once apparent when protamine insulin is substituted for regular insulin; indeed, for the first few days a larger number of units may be necessary, or a daily dose of protamine insulin as large as the number of units of regular insulin used before must be supplemented with additional regular insulin. This is because the action of the protamine preparation is retarded so that the full effect of the dose given on the first and second days is not obtained. My colleagues and I have found that the substitution can be made satisfactorily if four tenths of the previous dose of regular insulin is administered on the first day as a supplement and two tenths of the previous dose on the second day. Later, the number of units of protamine insulin usually can be reduced. Campbell [33] recommended giving from 75 to 100 per cent of the previous dose of regular insulin as protamine insulin in a single morning dose, accompanied the first day with about 60 per cent of the previous dose of regular insulin and on the second with 30 per cent of the previous dose.

Effectiveness of Protamine Insulin in Severe Acidosis: It seemed at first that the retarded action of protamine insulin made it undesirable for the treatment of coma, infection and other emergencies in which quick action is important. This is not strictly true, as was shown by Rabinowitch and his colleagues and as is indicated by experience at the Mayo Clinic. Recently 75 units of protamine insulin was given to a patient aged 28 years with diabetes of twelve months' duration who was admitted to the hospital in his first attack of severe diabetic acidosis. The carbon dioxide-combining power of the blood was 17 volumes per cent, and the sugar content was 288 mg. per hundred cubic centimeters. No more insulin was given for twenty-four hours and, with the exception of rest in bed and careful nursing, no other treatment. In eighteen hours the sugar value was 72 mg., and the value for the carbon dioxide-combining power of the blood had risen to 32.4 volumes per cent. In this case, as in 2 cases described by Rabinowitch, there obviously was not a bad prognosis originally. The patient later was nicely stabilized with 30 units of protamine insulin daily.

In cases of greater severity diabetic acidosis demands a more vigorous attack, but even so the supplementary use of protamine insulin seems to be highly desirable. Recently at the Mayo Clinic it has been made a practice to give from 50 to 100 units without delay, the patient being treated thereafter in the conventional manner with such multiple doses of regular insulin as seemed to be required from examinations of the blood sugar and tests of fractional specimens of the urine. The relative promptness with which patients later can be stabilized on reasonably small doses of insulin has been impressive in the last 10 cases of diabetic acidosis in which patients were treated by this procedure. Similarly, insensitivity to insulin after a major surgical operation has been avoided to a great extent when protamine insulin was given before and after the operation.

Hypoglycemic Reactions Following the Administration of Protamine Insulin: The subject of reactions is unduly minimized in many of the reports on the use of protamine insulin. Reactions usually occur less frequently than with other forms of insulin, and the experienced patient, as a rule, is given a longer period of warning before the reaction becomes severe, although exceptions occur. I am informed of 1 death following the use of protamine insulin, and I fear that others will follow unless great pains are taken to impress patients with the importance of heeding early symptoms and combating them with carbohydrate. Muscular exertion is particularly likely to provoke reactions in a patient maintained with protamine insulin. This adds to the difficulty of treatment and demands either careful regulation of exercise or the administration of extra carbohydrate before and after unusual exercise.

The prodromes of reaction differ from those with which patients and physicians using regular insulin have become accustomed. Those symptoms which probably have been correctly attributed to the protective mobilization of epinephrine are less pronounced. The sugar level falls so gradually that the adrenal glands seem not to be aroused. Thus, tremor, sweating, tachycardia and a pounding pulse may be missing; and symptoms of cerebral origin, such as drowsiness, headache, nausea and fatigue, become the only criteria of hypoglycemia. This adds to the confusion, because such symptoms resemble those of diabetic acidosis. Vomiting has occurred in a number of cases, especially with reactions that occurred at night or were combated tardily. Those writing on the subject have emphasized the fact that reactions following the administration of protamine insulin are likely to be prolonged or to recur after treatment as more and more of the insulin suspension is dissolved and mobilized. It is well to tell the patient always to carry small cubes of loaf sugar with him or "life savers" (a fruit-flavored "life saver" weighs 2.5 Gm.) and to take one cube of sugar or one candy at the first

suggestion of any unusual symptom, and another every twenty or thirty minutes until the next meal if symptoms persist or recur.

A severe reaction may be encountered after injections of protamine insulin. In several instances the patient has awakened in the morning with sore, stiffened muscles and a bitten tongue, and attacks with convulsions have been observed. Furthermore, long-continued hypoglycemia is not without peril, even if symptomless. I have referred to a study (fig. 2) in which 70 units of insulin was given and food was withheld. The patient, a volunteer, was a vigorous young adult with diabetes. The sugar content remained in the neighborhood of 50 mg. per hundred cubic centimeters for the last forty of the fifty-seven hours, but there were no symptoms (possibly because rest in bed was enforced) until the end of the period. The tendon reflexes then became exaggerated, and headache and mental confusion developed. The administration of dextrose relieved these abnormalities but not for several hours. Bollman [35] gave protamine insulin to dogs in sufficient doses to maintain long-continued hypoglycemia and, observing no symptoms other than drowsiness for fifty or sixty hours, then gave dextrose and found under those circumstances that fatal convulsions ensued. Animals that died during these attacks showed multiple petechial hemorrhages scattered throughout the brain.

Patients with Severe Diabetes Difficult to Treat Successfully: The unstable diabetic patient continues to be unstable even when given protamine insulin. This is particularly true of patients with diabetes of great severity who have been treated for many years with regular insulin. Allen [36] commented on this in his discussion of papers by Campbell and Joslin. He stated that he selected intentionally a large proportion of cases of the most difficult diabetes in which the sugar level was most labile, and he was unable to obtain satisfactory regulation with protamine insulin, either alone or in conjunction with old insulin. Campbell,[37] in the same discussion, agreed that certain patients presented extreme difficulties but said that although it might take a longer time to attain a satisfactory balance in such cases, this had been accomplished in all his cases up to that time. In a number of cases of severe diabetes at the Mayo Clinic it has not been possible to maintain the urine continuously free from sugar without danger of reaction, and in such cases it has seemed to be safer to permit the intermittent excretion of some sugar. Even with this less satisfactory management the patients for the most part seemed to feel healthier and stronger than they had before. In some cases adjustment was difficult at first but later was not so

34. Footnote deleted by the author.

35. Bollman, J. L.: Personal communication to the author.

36. Allen, F. M.: Tr. A. Am. Physicians **51**:186, 1936.

37. Campbell, W. R.: Tr. A. Am. Physicians **51**:187, 1936.

difficult. Bertrand Smith also has had this experience and suggested "that a glycogenic function that has become somewhat adjusted to the more acute effect of regular insulin may be slow in adaptation to the more gradual effect of the protamine preparation."

The General Health of Patients Receiving Protamine Insulin: Joslin,[10b] Smith,[13] Campbell [33] and several other clinicians have commented on the improved health of patients receiving protamine insulin. Rabinowitch [8b] observed a diminution in the bilirubin content of the serum. In one group of cases the bilirubin was 1.26 mg. before and 0.35 mg. per hundred cubic centimeters after the new treatment was begun. He found also that the cholesterol content of the blood was diminished in patients who showed any elevation of it on previous treatment with regular insulin. Hanssen [38] reported that the enlarged (fatty?) livers of diabetic children and young adults diminished in size, and similar observations have been made by Winnett and Bowcock. Joslin [10b] and also Campbell [33] have expressed the hope that the degenerative complications of diabetes could be prevented by the uninterrupted action of insulin on patients treated with protamine insulin. Priscilla White,[39] discussing recent progress in the treatment of severe diabetes, made the following comment:

> Whether one adheres to the theory that the high blood sugar or the high blood fat is responsible for complications in diabetes, the new preparation conquers both. In all probability the severe diabetic who in 1950 will have survived fifteen years of the disease may present a picture quite different from that of the long duration diabetic whom we have presented today.

Salt in the Treatment of Diabetes.—In this review last year attention was directed to the observations of Glass and Beiless and those of McQuarrie and his colleagues, which MacLean and I were in part able to confirm, namely, that salts of sodium, particularly sodium chloride, reduce the requirement of diabetic patients for insulin. A preliminary report by Sandstead [40] has just appeared, adding further confirmation and supplying the additional significant observation that ischemic pain and other neurocirculatory disturbances were affected to a strikingly satisfactory degree by treatment with salt. Sandstead studied 8 diabetic subjects for periods of from two to twelve months. Sodium chloride was given orally in doses of from 10 to 90 Gm. daily, and in every instance it exerted a depressing effect on the sugar level of the blood and made it possible either to reduce the dose of insulin considerably

38. Hansen, P.: Enlargement of the Liver in Diabetes Mellitus, J. A. M. A. **106**:914-916 (March 14) 1936.

39. White, Priscilla: Recent Progress in Severe Diabetes, Canad. M. A. J. **35**:153-161 (Aug.) 1936.

40. Sandstead, H. R.: The Effects of Oral Administration of Sodium Chloride in Diabetes, Hosp. News **3**:1-11 (Nov. 1) 1936.

or to increase the diet or both. Ill effects were not demonstrable, and, contrary to a common belief that salt raises the blood pressure, the blood pressure was not raised in any instance. In 1 case of the type in which there was relative insensitivity to insulin, the dose of insulin was ultimately reduced from 124 to 35 units, without any other change in the diet.

The most important aspect of the report of Sandstead is that bearing on the influence of this treatment on neurocirculatory disturbances. Five patients had demonstrable arteriosclerosis; the diabetes had been present over periods varying between several months and several years. Four of these patients were complaining of the pain of diabetic neuritis, for which treatment in general has been very unsatisfactory. All were relieved of this pain, 1 in a few days, 1 in two weeks, 1 in three weeks and 1 in a month. It should be pointed out that the pain of diabetic neuritis often disappears more or less spontaneously in time. Nevertheless that 4 patients should find this degree of relief so promptly after beginning the treatment is of significance. A histamine flare test was made as a routine procedure on the legs as a means of determining the degree of capillary dilatability. In 1 of the 4 cases the test showed completely negative results before treatment as high as the knees, whereas a good response was obtained later as low as the feet.

Diagnosis of Diabetes.—The diagnosis of diabetes ordinarily is not thought to present serious difficulties. The cardinal symptoms seen in the cases of more severe untreated diabetes often are pathognomonic, and the presence of reducing substances in the urine is suggestive in all cases and prompts further investigation. Exton [41] maintained, however, that more mistakes are made than is supposed and that they are of two kinds: failure to make a diagnosis of diabetes and the making of a false diagnosis of diabetes mellitus. Whenever the test for reducing substances in the urine gives positive results, a determination should be made of the cause of the reduction, and if this is dextrose, a dextrose tolerance test should be made.

A new method of analyzing sugar quantitatively, which was used by Exton with six standard confirmatory methods, in reducing urine from 1,000 men and women, revealed that while dextrose caused 97 per cent of the 200 reductions in which the value, if expressed as dextrose, exceeded 1 per cent, it caused only 60 per cent of the 800 reductions in which the value was 1 per cent or less. As his experience had shown that 10 per cent of the cases in which dextrose was the reducing substance proved to be cases of renal or some other form of nondiabetic dextrosuria, it followed that only half the 800 specimens of urine con-

41. Exton, W. G.: Differential Diagnosis of Conditions Associated with Sugar Excretion, New York State J. Med. **36**:1545-1553 (Oct. 15) 1936.

taining 1 per cent or less of reducing substances indicated the presence of diabetes.

Analysis of the 400 cases in which the reduction was not from dextrose revealed interesting facts. In 73 per cent the reducing substances were multiple: In 13.8 per cent they could not be identified, in 7.1 per cent glycuronic acid was responsible, in 2.1 per cent pentose, in 1.8 per cent fructose, in 1.6 per cent vitamin C and in 0.6 per cent galactose. Recent employment of vitamin C in pharmaceutic form suggests that this will be found in the future more often than in the past. The figures for pentose and fructose bear out the supposition that pentosuria and fructosuria occur more frequently than is indicated in the literature. Other data of interest are included in the article and also a description of the "one-hour-two dose dextrose tolerance test" proposed by Exton as being simpler and more informative than the test for sugar tolerance usually performed.

Experience with Exton's simplified dextrose tolerance test has been favorable. It has now become a routine procedure at the Mayo Clinic, but my colleagues and I do not agree with Exton that it entirely avoids equivocal results; hence when the interpretation is doubtful, we repeat the examination, using a standard procedure. Also, we cannot agree with Exton when he insists that a dextrose tolerance test is indicated whenever the cause of the reduction of reducing urine is demonstrated to be dextrose. If the value for sugar in the blood is greater than 130 mg. per hundred cubic centimeters in the morning before the ingestion of food, we regard the diagnosis of diabetes as established. The non-dextrose reducing substances found in urine do not provoke this degree of postabsorptive hyperglycemia. We reserve the dextrose tolerance test, therefore, for cases in which the sugar content of the blood in the morning is less than 130 mg. per hundred cubic centimeters, thereby avoiding possible injury to patients who may have diabetes of greater severity than is immediately apparent.

Acidosis and Coma.—Experience in the Mayo Clinic in 108 consecutive cases of severe diabetic acidosis was reported in this journal by Baker.[42] An interesting problem in connection with the subject is the nature and reason for the abdominal pain with spasm of the abdominal muscles, which so frequently leads to the fear, if not to an erroneous diagnosis, of an acute intra-abdominal disease. Walker[43] treated a patient with diabetic acidosis by giving 1,000 cc. of a 0.9 per cent solution of sodium chloride together with 50 units of insulin. As frequently

42. Baker, T. W.: A Clinical Survey of One Hundred and Eight Consecutive Cases of Diabetic Coma, Arch. Int. Med. **58**:373-406 (Sept.) 1936.

43 Walker, Harry: The Etiology of Abdominal Pain in Diabetic Acidosis, Ann. Int. Med. **9**:1178-1181 (March) 1936.

has been observed before, the severity of the abdominal pain began to lessen sooner than could be expected from any change produced by insulin. It lessened immediately, and within forty-five minutes had entirely disappeared. At the same time the abdomen lost its rigidity and became soft. Walker compared this observation to what is seen in heat cramps and gastric tetany. In both of them, as in diabetic acidosis, loss of chloride (and sodium) occurs. In heat cramps it results from perspiration; in gastric tetany, from vomiting and diuresis. In all three of these conditions spasm and pain affect muscles which are in action. In all of them relief from pain is promptly accomplished by restoring the lost electrolytes.

The same comments apply to the crisis of Addison's disease, in which loss of chloride and sodium also occur. Epigastric pain is an outstanding symptom and prompt relief usually is secured by administering intravenous injections of solution of sodium chloride. It appears that the pain in all these conditions may be attributed to the ischemia which results from the cramping of muscles and that the cramping is limited to actively contracting muscles. In diabetic acidosis and in Addison's disease the principal working muscles, aside from those of the heart, are those of respiration, and muscle spasm and consequent pain are limited usually to the muscles of respiration. This subject deserves more intensive investigation than has been devoted to it thus far.

Dillon, Riggs and Dyer [44] examined the brain in 8 fatal cases of uncomplicated diabetic coma and observed dilatation of the capillaries, perivascular edema, proliferation of the neuroglia and degeneration of the ganglionic cells. These abnormalities were most conspicuous in those parts of the brain which have been shown to be most susceptible to anoxemia produced by acute exsanguinating hemorrhage or by heart failure. Furthermore, the lesions were like those noted after acute asphyxia. In diabetic coma the total volume of the blood is reduced by hemoconcentration to a degree comparable to that in severe hemorrhage, and severe myocardial damage frequently accompanies it. Thus, it seemed to the authors that the abnormal physiology of diabetic coma is a reduced volume of circulating blood, a consequent marked reduction of blood pressure, both systolic and diastolic, limitation of the amount of blood flowing to the head and resulting anoxia of the brain. The cerebral lesions, in turn, may further embarrass the cardiac function by paralysis of the vasomotor and other vegetative centers, and in consequence the patient may die as a result of collapse of the vasomotor system or failure of the respiratory function, even when chemical estimation of the degree of acidosis indicates an improvement.

44. Dillon, E. S.; Riggs, H. E., and Dyer, W. W.: Cerebral Lesions in Uncomplicated Fatal Diabetic Acidosis, Am. J. M. Sc. **192**:360-365 (Sept.) 1936.

Tuberculosis and Diabetes.—The outlook for patients with diabetes complicated by tuberculosis is by no means as hopeless as has been supposed. Unfortunately, until recently, the staff physicians of many hospitals for tuberculous patients have not been prepared to provide expert control of the metabolic abnormality of these patients. Myers and McKean [45] in a small series of cases (80) obtained arrest or apparent arrest of tuberculosis in 21 per cent of the cases in which it was moderately advanced, in 25 per cent of those in class 3B and in 10 per cent of those in class 3C. Eventual arrest was anticipated in an additional 43 per cent of cases in class 2 and in another 16 per cent of those in class 3B. The results compared favorably with those for nondiabetic patients with tuberculosis of like severity in the same hospital. The tentative conclusion was reached that as long as the diet and insulin are regulated, coexisting diabetes does not have an adverse effect on the course of pulmonary tuberculosis. The average amount of insulin needed to bring the patients under control on admission was 46 units daily. The average dose at the time of dismissal was 42 units daily. The average diet contained 108 Gm. of carbohydrate, 62 Gm. of protein and 162 Gm. of fat. In its relatively low amount of protein, its caloric content and its relatively high fat and carbohydrate ratio it was similar to that which McCann and Barr [46] found to be most suitable in cases of uncomplicated pulmonary tuberculosis.

A Public Health Problem.—The increasing mortality among persons with diabetes is portrayed graphically in a recent bulletin of the Metropolitan Life Insurance Company.[47] If the present trend is maintained, the relative positions of tuberculosis and diabetes as causes of death will be reversed within a decade. In one state, Nebraska, this has already occurred. In the four adjacent states (Iowa, Kansas and the Dakotas) the diabetes rate for 1933-1934 was close to that of tuberculosis, and in twelve of ninety-three cities of 100,000 population or more it was higher. Outstanding among communities in which this was found to be the case were Syracuse, N. Y., where the deaths among subjects with diabetes were 60.9 per cent in excess of those among subjects with tuberculosis; New Haven, Conn., with an excess of 43.7 per cent, and Rochester, N. Y., with an excess of 42.4 per cent. In the city of New York as a whole the deaths credited to diabetes were slightly less than half the total charged to tuberculosis, but in Brooklyn, N. Y., they were only

45. Myers, G. B., and McKean, R. M.: Diabetes and Tuberculosis: I. An Analysis of Eighty Cases from the Standpoint of Tuberculosis, Am. Rev. Tuberc. **32**:651-664 (Dec.) 1935.

46. McCann, W. S., and Barr, D. P., quoted by Myers and McKean.[45]

47. The Comparative Mortality from Diabetes and Tuberculosis, Stat. Bull. Metropolitan Life Ins. Co. **17**:6-9 (Feb.) 1936.

3.1 per cent less. The implication of these figures is obvious. The subject will demand more and more attention from public health officials. The wise suggestion is made that groups which have been organized to combat tuberculosis extend their work to the study and control of diabetes and other chronic diseases. It is much better to use established agencies for this purpose than to create new ones, and the problems presented by diabetes from the point of view of control have many aspects in common with those of tuberculosis. This idea has already taken hold in several parts of the country and should be encouraged.

Theory of Diabetes.—Sensitivity to Insulin: Attention was directed in an earlier review [48] to the studies of Falta and his associates on the resistance to insulin encountered in some cases of diabetes. The subject has been studied also by several other investigators, and Himsworth, of London, and MacBryde, of St. Louis, have presented data of experiments that may affect therapeutic procedures. The observations of Himsworth [49] have appeared in British medical journals since 1932; they are summarized in his recent discussion before the Royal Society of Medicine. The extent to which the sugar content of the blood of healthy young men was lowered by a standard dose of insulin, administered by vein, was increased when the previous diet had been high in carbohydrate and decreased when the previous diet had been low in carbohydrate. These effects of a varying amount of dietary carbohydrate are not to be explained, he said, either by a difference in the reaction (p_H) of the tissues or by ketosis; and since the increased activity of insulin after carbohydrate feeding also was observed when the carbohydrate was given as dextrose by vein, it seemed unlikely that any hormone from the digestive tract, such as the "duodenin" described by Laughton and Macallum, could be a factor. Himsworth [50] thus reached the conclusion that the same dietetic factors which improve sugar tolerance in normal men also increase sensitiveness to insulin.

That more carbohydrate in the diet will increase and less carbohydrate will decrease the sugar tolerance of normal men was demonstrated independently by Adlersberg and Porges [51] and by Sweeney.[52]

48. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **55**:304-343 (Feb.) 1935.

49. Himsworth, H. P.: Discussion of Physiological Factors Influencing the Action of Insulin, Proc. Roy. Soc. Med. **29**:658-662 (April) 1936.

50. Himsworth, H. P.: The Influence of Diet on the Sugar Tolerance of Healthy Men and Its Reference to Certain Extrinsic Factors, Clin. Sc. **1**:251-264 (Nov. 14) 1934.

51. Adlersberg, D., and Porges, O.: Zur Theorie und Praxis der kurativen Diabetesbehandlung, Klin. Wchnschr. **5**:1451-1455 (Aug. 6); 1508-1513 (Aug. 13) 1926.

52. Sweeney, J. S.: Dietary Factors That Influence the Dextrose Tolerance Test: A Preliminary Study, Arch. Int. Med. **40**:818-830 (Dec.) 1927.

The interpretation of this, until recently, was that the higher tolerance after a high carbohydrate diet, as measured by dextrose tolerance tests and after preliminary injections of dextrose, was attributable to a greater sensitiveness of the pancreas, with a resultant more rapid or increased secretion of insulin. However, Dann and Chambers [53] showed that in dogs which had fasted for from fifteen to thirty days the administration of dextrose caused little rise in the respiratory quotient and that when insulin was injected at the same time, little more dextrose was oxidized. This demonstrated apparently that the diminished sugar tolerance after starvation (in which the metabolism is largely at the expense of fat) was not due merely to the lack of insulin. Important also in this connection is the work of Soskin,[54] to which reference was made in our last review. It does not disprove the previous contention that sugar stimulates a greater excretion of insulin; it suggests rather that more than one effect is produced.

Himsworth [55] showed further that the increased tolerance and increased activity of injected insulin, effected by feeding more carbohydrate to normal men, did not depend on the caloric value of the intake of food or on the ketogenic-antiketogenic ratio or on the fat content of the diet but rather on the absolute amount of carbohydrate. The quantitative nature of his experiments permitted the construction of curves to express the relationship of variation in the carbohydrate fed to change either in the dextrose tolerance or the sensitivity to insulin. He called these curves the "determination curve of glucose tolerance" and the "determination curve of insulin sensitivity." He found that the two had exactly the same form. He found also that when the change in the dextrose tolerance was plotted against the change in the sensitivity to insulin, a straight line was obtained, inclined 45 degrees to the horizontal, and from these observations he concluded that "the change in glucose tolerance consequent upon variation in the carbohydrate content of the diet is completely accounted for by change in the sensitivity to insulin secreted by the pancreas," thus excluding the necessity for assuming the secretion of more insulin by the pancreas.

Those readers who have had much experience with dextrose tolerance tests will remain skeptical as to whether blood sugar-time curves can safely be subjected to such precise mathematical analysis; and even granting that "the method of areas" employed by Himsworth is a step

53. Dann, M., and Chambers, W. H.: Animal Colorimetry: Metabolism of Glucose Administered to Fasting Dog, J. Biol. Chem. **89**:675-688 (Dec.) 1930.

54. Soskin, S.; Allweiss, M. D., and Cohn, D. J.: Influence of the Pancreas and the Liver upon the Dextrose Tolerance Curve, Am. J. Physiol. **109**:155-165 (July) 1934.

55. Himsworth, H. P.: The Dietetic Factor Determining the Glucose Tolerance and Sensitivity to Insulin of Healthy Men, Clin. Sc. **2**:67-94 (Sept. 30) 1935.

in the direction of accuracy of interpretation, it still may be doubted whether the results are as extremely accurate as Himsworth claimed. In any event, the case for relationship between the carbohydrate of the diet and the sensitivity to insulin is good and provides another explanation for the beneficial effects of diets high in carbohydrate in certain cases of diabetes. This provides also a rationale for treating diabetic coma with large doses of dextrose, as advocated by Ellis and referred to in an earlier review.[56]

Himsworth,[57] in 1934, showed with animals that the degree to which insulin suppressed hyperglycemia, produced by the administration of dextrose intravenously, was proportional to the sensitivity of the animal to insulin. By subjecting diabetic patients to this test he was able to distinguish two types of patient: In one, the "insulin-sensitive" type, injected insulin suppressed the hyperglycemia provoked by dextrose administered by mouth; in the other it failed to do so. The reaction of the "insulin-sensitive" diabetic patient to dextrose and insulin was like that obtained in healthy subjects, but the reaction of the "insulin-insensitive" diabetic patient was abnormal. In the former, hyperglycemia was prevented; in the latter it was not.

Himsworth's inquiry then was directed to discover why the action of insulin was impaired in the type of diabetic patient insensitive to insulin and to determine whether this impairment was due to derangement of hepatic function or to inhibition of the action of insulin in the periphery. For this purpose comparison was made of the content of sugar in arterial blood (blood flowing freely from the lobe of the ear) and that in blood drawn simultaneously from a vein. This co-called arteriovenous difference normally was moderately increased when dextrose was administered to normal subjects, and when insulin was given with the dextrose the arteriovenous difference amounted to as much as 30 or 40 mg. per hundred cubic centimeters of blood. With diabetic patients of the "insulin-sensitive" type, the response to this test was like that of normal subjects, whereas with those of the "insulin-insensitive" type, the response was minimal, indicating inhibition of the peripheral action of insulin. Soskin and his associates,[54] although agreeing with Himsworth that the pancreas does not secrete an increased amount of insulin after the injection of dextrose, disagreed with him in attributing importance to the activity of insulin in the periphery. They considered that differences between the values found for sugar in arterial and in venous blood are of no significance unless they first are corrected for rate of blood flow and hydration.

56. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **57**:422-471 (Feb.) 1936.

57. Himsworth, H. P.: Diabetes Mellitus: Its Differentiation into Insulin-Sensitive and Insulin-Insensitive Types, Lancet **1**:127-130 (Jan. 18) 1936.

In any case, Himsworth [57] was led to suggest that the diabetes of the "insulin-sensitive" type of patient was attributable to lack of insulin, whereas that of the "insulin-insensitive" type of patient was due not to lack of insulin but to insensitivity to insulin. This he correlated with the observed action of carbohydrate on sugar tolerance. "Insulin-sensitive" patients tolerated large increases in dietary carbohydrate without requiring an increased dose of insulin, but "insulin-insensitive" patients showed glycosuria after only slight increases in the dietary carbohydrate: "The insulin-sensitive diabetic thus apparently reacts like the normal subject by becoming more sensitive to insulin as the dietary carbohydrate increases, whilst giving more carbohydrate administered to the insulin-insensitive does not evoke this reaction." [49]

Himsworth [49] has offered two explanations of this variability of sensitiveness to insulin. He first assumed that an activator was involved, an insulin kinase, the action of which was complementary to that of insulin. Later, the studies of Marks,[58] to be referred to presently, suggested to Himsworth the view that the variation may be accounted for by the presence of more or less of some antagonist to insulin.

MacBryde's [59] study of a group of diabetic patients led to the conclusion at which Himsworth arrived, namely, that diabetic patients fall into two types, one sensitive to insulin and the other relatively insensitive. The distinguishing criteria differed, however. He tested the response to an injection of 1 unit of insulin for each 10 pounds (4.5 Kg.) of body weight and found that some patients showed a marked fall in the sugar content of the blood, whereas others showed relatively little response. He also tested the tolerance to overdoses of insulin and observed that those patients showing sensitivity by the first test would tolerate little or no increase in the dose of insulin above the daily requirement, whereas those who were resistant according to the first test could tolerate large overdoses, in some cases as much as 60 units or more. He tested also the number of grams of dextrose metabolized per unit of insulin and found in patients sensitive to insulin that this ranged from 1 to 3 Gm., whereas in those insensitive to insulin it was less than 0.5 Gm. MacBryde's patients who were sensitive to insulin, however, failed to gain tolerance with a higher carbohydrate diet, there being only 1 exception among 8 patients, whereas his "insulin-insensitive" patients (he used the term "insulin resistant")

58. Marks, H. P.: The Pituitary Factor, Proc. Roy. Soc. Med. **29**:663-666 (April) 1936.

59. MacBryde, C. M.: Response to Insulin as an Index to the Dietary Management of Diabetes, J. Clin. Investigation **15**:577-589 (Sept.) 1936; Advances in the Dietary Management of Diabetes, South. M. J. **29**:488-491 (May) 1936.

gained tolerance on a high intake of carbohydrate. This is exactly opposite to what Himsworth [57] observed; and thus what seemed to promise a means of harmonizing the clinical practice of those advocating a diet high in carbohydrate and those recommending a diet high in fat only adds to the existing confusion.

The position of those clinicians who are adhering to a course between the extremes of a diet high in fat and a diet high in carbohydrate seems to be supported by Himsworth's [55] "insulin sensitivity determination curve," to which I have referred. This curve shows that in a normal subject a rise in sensitivity to insulin and consequently an improvement in the ability of the body to dispose of carbohydrate occur as the dietary carbohydrate is increased from 50 to 200 Gm. a day but that little increase in sensitivity occurs when the dietary carbohydrate is increased beyond 200 Gm. until the amount of 350 Gm. is exceeded, when another but more moderate increase of sensitivity is observed. In other words, the best effectiveness of insulin and the maximal disposal of dietary carbohydrate by each unit of insulin seem to be obtained when the diet contains 200 Gm. of carbohydrate. Below this allowance further addition of carbohydrate demands a proportionately small increase of insulin, whereas above this allowance a relatively larger increase of insulin is needed. Himsworth seemed to lay less emphasis on the significance of this "insulin sensitivity determination curve" than I have; at least I am led to judge so by the fact that he advocated the use of a diet containing much more than 200 Gm. of carbohydrate. He even stated the opinion that a diet in which the carbohydrate represents less than 50 per cent of the total calories may cause progressive permanent impairment of sugar tolerance, so that in the course of time diabetes mellitus results.

Himsworth has published two articles on statistics regarding diabetes in support of this contention. In one of these he and Marshall [60] attempted to show that most diabetic patients selected a diet low in carbohydrate before diabetes developed. In the other [61] he pointed to a correlation between the dietary habits of persons in various communities and countries and the diabetic mortalities. These statistical articles are not good. The difference between the diets of diabetic patients before they had diabetes and of the group of nondiabetic patients is slight, and the difference between the amount of carbohydrate included in diets in certain states of the United States with a high incidence of diabetes and in others with a lower incidence also is not enough to impress any one who does not wish to believe that this is the explana-

60. Himsworth, H. P., and Marshall, E. M.: The Diet of Diabetics Prior to the Onset of the Disease, Clin. Sc. **2**:95-115 (Sept. 30) 1935.

61. Himsworth, H. P.: Diet and the Incidence of Diabetes Mellitus, Clin. Sc. **2**:117-148 (Sept. 30) 1935.

tion. For instance, the death rate from diabetes in the state of Maine was 25.5 per hundred thousand, whereas that of the adjacent province of Quebec was 11; that of the United States as a whole was 20, and that of Canada as a whole was 12. It may be true that the inhabitants of the United States eat more fat and therefore less carbohydrate than do people in Canada, but Himsworth's own experiments show that differences in carbohydrate consumption between the gross values of 200 and 350 Gm. are of little consequence in the sensitivity of healthy subjects to insulin (their own insulin). The sharp slopes of his "insulin sensitivity determination curve" occur, as I have stated, when the amount of carbohydrate is changing from 50 to 200 Gm., and when it exceeds 350 Gm. It is doubtful whether many persons, either in Maine or in Quebec, eat less than 200 Gm. or more than 350 Gm. of carbohydrate a day.

There are far too many inestimable factors to justify any conclusion today as to why diabetes is so unequally distributed over the world, or as to why there is so much more diabetes (death from diabetes) in the northern tier of states of the United States than in the southern tier or in the provinces of Canada. A factor which seems more important than the difference in the consumption of carbohydrate by these respective populations is that disclosed by the observations of Petersen [62] and, independently, those of Mills.[63] This, namely, is a correlation between the incidence of death with diabetes and the frequency and severity of changes in the weather (temperature, barometric pressure, humidity, ionization of air and so forth). The northeastern and north central states of the United States are in the track of the major cyclonic disturbances. These storms acquire their greatest severity as they sweep eastward from Montana to the northeast. The weather of the Canadian provinces is much less affected by them, and the states south of the Ohio River lie south of this storm track.

The Rôle of the Hypophysis in Carbohydrate Metabolism.—I have mentioned that Himsworth seemed to be prepared to abandon his early assumption of an insulin activator (kinase) in favor of an inhibitor and that he has been influenced in this by the results of investigations by Marks.[58] Marks, with Best, Dale and Hoit, confirmed the observation of Mann and Magath that sugar disappears from the blood in animal preparations when the influence of the liver is excluded and

62. Petersen, W. F., and Milliken, M. E.: The Patient and the Weather: The Footprint of Asclepius, Ann Arbor, Mich., Edwards Brothers, Inc., 1935, vol. 1, pt. 1; Autonomic Integration, 1936, vol. 1, pt. 2; Autonomic Dysintegration, 1934, vol. 2.

63. Mills, C. A.: Health and Disease as Influenced by Climatic Environment, Internat, Clin. **2**:143-167 (June) 1936; Diabetes Mellitus: Is Climate a Responsible Factor in the Etiology? Arch. Int. Med. **46**:569-581 (Oct.) 1930.

that injections of insulin accelerate the rate of this disappearance. They could account quantitatively for the sugar; it was mainly stored in the muscles as glycogen. In the intact animal when the blood sugar falls after an injection of insulin, it is restored again by the conversion of hepatic glycogen into dextrose in response to stimulation of the liver by epinephrine. This has been demonstrated repeatedly. It now appears that if the hypophysis is removed from the animal, the percentage of sugar produced in the blood by a small dose of insulin is not corrected; the sugar content continues to fall until the animal dies in convulsions. This occurred, as was demonstrated by the experiments of Cope and Marks,[64] even when the liver was abundantly supplied with glycogen, as well as under conditions in which the compensatory secretion of epinephrine was found to take place just as it does in a normal animal. The conclusion followed that the absence of the hypophysis leads to a greater stability of hepatic glycogen. Supportive evidence was provided by experiments on the perfused livers of hypophysectomized frogs. In them glycogen was converted into sugar much less readily than in a normal animal.

The converse of this ineffective recovery from hypoglycemia of an animal deprived of its hypophysis also was observed. An abnormally intense secretion of dextrose by the liver, coupled with an exaggerated phase of recovery from hypoglycemia, followed injections of insulin when suitable extracts of the anterior lobe of the pituitary gland were injected. But apart from any action on the liver, these extracts of the anterior lobe also inhibited or delayed the peripheral action of insulin, as judged by observations on the arteriovenous differences of the sugar contents.

Marks[58] commented on the striking resemblances between these effects of extracts of hypophysis and those observed (by Himsworth) when the diets of normal subjects and diabetic patients contained varying amounts of carbohydrate. Marks, therefore, was led to suggest that the anterior lobe of the hypophysis is stimulated by an inadequate supply of carbohydrate. He suggested that the hypophysis is concerned in the production of carbohydrate from protein or fat or both and that the greatest demand is made on it when the organism, because of lack of available carbohydrate, is forced to obtain its necessary dextrose from protein or fat. Thus, when the diet is poor in carbohydrate, the hypophysis is stimulated, and the peripheral response to insulin is inhibited; and vice versa, when the diet is rich in carbohydrate, the hypophysis becomes inactive, the peripheral response to insulin is no longer inhibited and at the same time dextrose is less easily mobilized from the liver.

64. Cope, O., and Marks, H. P., quoted by Marks.[58]

In a previous review [48] (1935), when discussing the work of H. Locke, whose experiments led him to conclude that the hypophysis exerts its influence on carbohydrate metabolism by way of the central nervous system, I commented on the demonstration on cats by Davis and his associates that experimental lesions accurately placed in the hypothalamus would permit removal of the pancreas without the development of severe diabetes. The lesions were produced bilaterally by means of the Horsley-Clarke stereotaxic instrument. If Locke's observations were correct, it seemed to me that these cats should be resistant to injections of extracts of the anterior lobe of the hypophysis containing the blood sugar-raising (contra-insular) agent, and if this were found to be the case it would do much to establish the reliability of Locke's conclusions. This experiment has now been performed by Ingram and Barris.[65] Four of a group of 5 cats with lesions located in the suprachiasmal portion of the hypothalamus and including the filiform nuclei, failed to show normal responses to the blood sugar-elevating effect of a suspension of the anterior lobe of the hypophysis. The preparation caused hyperglycemia in normal cats. Three other cats manifested retarded responses to the action of much smaller doses. That the failure to respond actively to the suspension of the anterior lobe of the hypophysis was not due to a deficient supply of hepatic glycogen was established by removing samples of liver from the animals at the end of the periods of observation. The values for glycogen ranged from 3.09 to 5.51 per cent.

Ingram and Barris [65] expressed the opinion that the effect of lesions of the hypothalamus on carbohydrate metabolism could be interpreted in either of two ways: (1) that the site of action of the diabetogenic (contra-insular) hormone of the anterior lobe of the hypophysis was destroyed or (2) that injury to the hypothalamus had depressed the action of the anterior lobe of the hypophysis. Houssay had objected to Locke's conclusion that hormones of the anterior lobe of the hypophysis act by way of the hypothalamus, basing his criticism on the results of experiments on toads. Although Houssay and Biasotti [66] had found that lesions in the hypothalamus prevented or ameliorated diabetes, they had ascribed this result to the loss of some direct nervous influence on the anterior lobe of the hypophysis. Ingram and Barris refrained from drawing final conclusions. However, they pointed out that nerve connections between the hypothalamus and the anterior lobe

65. Ingram, W. R., and Barris, R. W.: Evidence of Altered Carbohydrate Metabolism in Cats with Hypothalamic Lesions, Am. J. Physiol. **114**:562-571 (Feb.) 1936.

66. Houssay, B. A., and Biasotti, A.: Hypophysektomie und Pankreasdiabetes bei der Kröte, Arch. f. d. ges. Physiol. **227**:239-250, 1931.

of the hypophysis, if there are any at all, are not well established and that their evidence that some hypothalmic lesions appear to depress the diabetogenic activity of active suspensions of the anterior lobe of the hypophysis supported the assumption of Locke that the site of action of the diabetogenic hormone is in the hypothalamus. They stated that the frequency with which bilateral atrophy or destruction of the filiform nuclei was associated with alteration of carbohydate metabolism was striking but that exceptions occurred (in 1 cat in which these cell groups were destroyed the response to the hyperglycemic activity of suspensions of the anterior lobe of the hypophysis was entirely normal) and therefore that the matter of more exact localization of the areas concerned must await further study.

The idea that diabetes mellitus depends on uncontrolled activity of the anterior lobe of the hypophysis is supported by the fact that injections of an estrogenic substance alleviate to some extent the symptoms of diabetes in depancreatized dogs (Barnes, Regan and Nelson, 1933). This has been observed also in some instances of diabetes mellitus by Mazer, Meranze and Israel [67] and Houssay [68] but was not found by Collens and his associates.[69] Also, de Wesselow and Griffiths [70] recently have reported that injections of blood plasma from a particular type of diabetic patient rendered rabbits less sensitive to insulin, much as would an injection of extract of the anterior lobe of the pituitary gland. The possibility was entertained that this type of diabetic patient corresponds to the "insulin-insensitive" type of Himsworth.

In this connection Young [71] offered the following contribution: Mention has been made of the observation by Cope and Marks that injection into rabbits of a saline suspension of the anterior lobe of the pituitary gland was followed by resistance to the action of insulin and increased sensitivity to the hyperglycemic effect of epinephrine. Young [72] investigated the factor responsible for these effects and found it to be closely associated, if not identical, with the lactogenic hormone. Incidentally, the lactogenic hormone is now being considered as iden-

67. Mazer, Meranze and Israel, quoted by Young.[71]

68. Houssay, B. A., quoted by Young.[71]

69. Collens, W. S.; Slo-Bodkin, S. G.; Rosenbliett, Sidney, and Boas, L. C.: The Effect of Estrogenic Substance on Human Diabetes, J. A. M. A. **106**:678-682 (Feb. 29) 1936.

70. deWesselow, O. L. V., and Griffiths, W. J.: On the Possible Rôle of the Anterior Pituitary in Human Diabetes, Lancet **1**:991-994 (May 2) 1936.

71. Young, F. G.: Glycogen and the Metabolism of Carbohydrate, Lancet **2**: 237-242 (Aug. 1); 297-302 (Aug. 8) 1936.

72. Young, F. G.: The Influence of Anterior Pituitary Extracts on the Glycaemic Response to Insulin and Adrenaline in Rabbits, J. Physiol. **87**:13P-15P (March 14) 1936.

tical with the adrenotropic hormone, which brings these observations into line with those of Long and Lukens,[73] to which reference will be made presently. Further exploration of this interesting possibility is awaited with interest. The period of lactation is a time when sugar is withdrawn from the blood at an accelerated rate; hypoglycemia threatens and sometimes develops in cows that are bred to produce milk abundantly. The association in one factor of a stimulant to lactation with an action on the liver and periphery, which increases the discharge of sugar from the former and diminishes utilization by the latter, would be highly purposeful.

Collip[74] has suggested that the diabetogenic action of extracts of the anterior lobe of the hypophysis is due to the combined effect of two substances, one acting on the level of the blood sugar and the other producing ketosis. Young[71] said he thought it possible that three substances are concerned: (1) a factor which stimulates the formation of glycogen in the liver and which may be associated with the ketogenic factor; (2) a glycotropic factor, which facilitates hepatic glycogenolysis and inhibits to some extent the peripheral action of insulin and (3) a glycogenolytic factor, causing hyperglycemia. Any of these alone is not diabetogenic, but their combined action would result in an increased production of sugar in the liver, ketosis and possibly in decreased utilization of sugar in the periphery. Hertz[75] has called attention to a possible relationship between von Gierke's disease and the hypophysis. This condition is characterized by the excessive formation of hepatic glycogen accompanied with ketonuria, and it would result from the first of the three factors mentioned. The extracts prepared by Young inhibited the action of insulin but did not produce ketosis or affect the level of the sugar in the blood during fasting. This is the second factor; the third presumably is a hormone producing more intense excretion of sugar by the liver. It seems rather unreasonable thus to multiply the number of hormones in the hypophysis; in time the observations probably will be explained more simply than this.

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73. Long, C. N. H.: The Interrelationships of the Glands of Internal Secretion Concerned with Metabolism, Am. J. M. Sc. **191**:741-759 (June) 1936; Disturbances of the Endocrine Balance and Their Relation to Diseases of Metabolism, Ann. Int. Med. **9**:1619-1627 (June) 1936. Long, C. N. H., and Lukens, F. D. W.: The Effects of Adrenalectomy and Hypophysectomy upon Experimental Diabetes in the Cat, J. Exper. Med. **63**:465-490 (April) 1936; The Effect of the Adrenotropic Fraction of the Anterior Pituitary upon the Glycosuria of Hypophysectomized-Depancreatized Cats, Am. J. Physiol. **116**:96, 1936; The Effect of Adrenalectomy upon the Fatty Infiltration of the Liver Following Total Pancreatectomy in the Cat, ibid. **116**:96-97, 1936.

74. Collip, J. B., quoted by Young.[71]

75. Hertz, W., quoted by Young.[71]

Significant as this newer work on the physiology of carbohydrate metabolism appears to be, clearly there is much to be learned before the results can be interpreted clinically. Woodyatt,[76] it is true, found that the administration of an extract of the anterior lobe of the hypophysis to diabetic patients might cause an increase of glycosuria. After the high dose was interrupted an improvement might occur comparable to that which follows removal of the hypophysis of animals with pancreatic diabetes. This is what should be expected. Acromegaly in its stages of activity frequently, but by no means always, is associated with (provokes?) diabetes. Clinical insufficiency of the anterior lobe of the hypophysis should increase the tolerance for sugar, and there is some evidence that it does (Goetsch, Cushing and Jacobson[77]), although a number of cases of hyperglycemia and glycosuria have been reported in patients with hypopituitarism, the last one being reported by Sexton and Neuhoff.[78] The diabetes was considered to be "of true pancreatic origin" by Sexton and Neuhoff, that is, "due to a deficiency in insulin," and its occurrence was considered to be "entirely independent of the pituitary syndrome." In my opinion in the large majority of cases diabetes is independent of any abnormality of the pituitary gland.

The Rôle of the Adrenal Glands in Carbohydrate Metabolism.—The observation of Buell, Strauss and Andrus[79] that lactic acid is produced only slowly by the autolyzing muscles of adrenalectomized rats, although the lactic acid content of the blood is known to be high in such animals. led them to the assumption that glycogenesis from lactic acid may occur less readily when the influence of the adrenal glands is removed. Other experiments support this assumption.[80] Known amounts of lactic acid neutralized with sodium hydroxide were given by stomach tube to (1) normal rabbits, (2) adrenalectomized rats insufficiently treated with adrenal cortex extract, (3) adrenalectomized rats treated only with salt solution and (4) adrenalectomized rats adequately treated with the cortical extract. The livers of each of the rats deprived of its adrenal glands and inadequately treated with adrenal cortex extract or treated

76. Woodyatt, R. T.: Tr. A. Am. Physicians **51**:123-127, 1936.

77. Goetsch, Emil; Cushing, Harvey, and Jacobson, Conrad: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri: An Experimental and Clinical Study, Bull. Johns Hopkins Hosp. **22**:165-190 (June) 1911.

78. Sexton, D. L., and Neuhoff, Fritz: Pituitary Infantilism with Diabetes Mellitus, Endocrinology **20**:856-859 (Nov.) 1936.

79. Buell, Strauss and Andrus, quoted by Buell, Anderson and Strauss.[80]

80. Buell, Mary V.; Anderson, I. A., and Strauss, Margaret B.: On Carbohydrate Metabolism in Adrenalectomized Animals, Am. J. Physiol. **116**:274-281, (July) 1936.

only with salt contained much less glycogen than the livers of normal rats subjected to identical conditions. At the same time the blood of these animals contained several times as much lactic acid as was found in the blood of normal rats, in spite of the fact that the amount of lactic acid absorbed from the bowel was in many cases less than that in the normal animals. In adrenalectomized rats adequately treated with adrenal cortex extract the liver was well supplied with glycogen, although the blood of these animals contained somewhat more lactic acid than was found in the blood of the normal rabbits. Thus, there appears to be another function of the liver under the regulation of the cortex of the adrenal glands. The analogous clinical disturbance should be looked for in Addison's disease. Possibly a test for this disease might be based on the rate at which a given dose of lactate is disposed of by the patient. In diabetic acidosis lactic acid tends to accumulate together with the keto-acids. Perhaps this may indicate that in severe acidosis the function of the adrenal glands is depressed. Certainly it is a fact that the amount of sugar excreted by a diabetic patient often diminishes after acidosis has developed. The sugar content of the blood is correspondingly decreased, and Evans [81] has proposed that the adrenal cortex has to do with the ability of the liver to convert protein into carbohydrate.

Reference has been made in previous reviews to the experiments of Long and Lukens [73] on cats from which both the pancreas and the adrenal glands were removed. These animals were treated with adequate doses of adrenal cortex extract and salt and survived for from two to four weeks. During this time they manifested as little evidence of diabetes as do animals after hypophysectomy. Particularly noticeable was the suppression of ketosis. The cortex rather than the medulla was thought to be necessary for the maintenance of the diabetic state in the depancreatized animals, because cats from which only the medulla of the adrenal glands and at a later date the pancreas were removed did not show any amelioration of the diabetic condition. Rather strangely, the administration of adrenal cortex extract prepared by the method of Swingle and Pfiffner did not aggravate the diabetes, as might be expected, even when large doses were given. This extract apparently does not contain that factor of the intact cortex of the adrenal gland which acts in carbohydrate metabolism, or at least does not contain much of it. Confirmation and extension of these observations, both with dogs and with cats, has been provided by Berg, Gross,

81. Evans, Gerald: The Adrenal Cortex and Endogenous Carbohydrate Formation, Am. J. Physiol. **114**:297-308 (Jan.) 1936.

Lowenberg and Zucker.[82] Their study indicated in their opinion that the adrenal gland as a part of an emergency reflex mechanism to prevent hypoglycemia is not required but that a factor derived from the cortex is necessary. In the adrenalectomized animal, in the absence of a naturally stored substance or of injected adrenal cortex extract, a sugar content of the blood depressed by insulin is not restored spontaneously, as is usual. The dose of extract in these experiments was from 2 to 5 dog units per kilogram per day, from two to five times the requirement for maintenance.

Long and Lukens [73] reported this year that an adrenotropic fraction of the anterior lobe of the hypophysis injected into cats from which both the hypophysis and the pancreas previously had been removed markedly increased the excretion both of dextrose and of nitrogen. The extract was obtained from Dr. Collip. Similar effects were obtained in cats both after feeding and after fasting, even when the animals were not exhibiting glycosuria at the time the injections were made. The volume of urine excreted usually was doubled. The amount of dextrose could be accounted for on the assumption that it was derived from the protein represented by the nitrogen. Equivalent amounts of the same extract injected into hypophysectomized and depancreatized cats from which the adrenal glands also had been removed was without effect. The interpretation given by the authors was that hypophysectomy probably results in this effect on experimentally produced diabetes by reason of the accompanying hypofunction of the adrenal cortex, but it is recognized that this is not proved. If this view is correct, the adrenal cortex must contain at least two hormones, one that appears to control the metabolism of sodium (or potassium) and another, at present a hypothetical entity, the function of which is particularly concerned with the production of dextrose from protein (and possibly with certain aspects of the metabolism of fatty acids and lactic acid). As yet no one has demonstrated the ability of extracts of the adrenal cortex to accentuate diabetic conditions in adrenalectomized and depancreatized animals, and until such time as this is accomplished the possibility still exists that adrenalectomy effects pancreatic diabetes by altering the normal secretory activity of the anterior lobe of the hypophysis.

Long and Lukens have successfully performed experiments involving astonishing technical difficulties. At several meetings during 1936 they have shown moving pictures illustrating cats that survived successfully and were maintained for many days with salts and adrenal cortex

82. Berg, B. N.; Gross, J.; Lowenberg, C., and Zucker, T. F.: The Adrenal Medulla and Cortex in Relation to Effects of Insulin, Arch. Path. **22**:283 (Aug.) 1936. Houssay, B. A., and Biasotti, A.: Influencia de la hipófisis y la suprarenal sobre la diabetes pancréatica del sapo, Rev. Soc. argent. de biol. **12**:104-111 (June) 1936.

extract after removal of the hypophysis, the pancreas and both adrenal glands. The period of survival and the good general condition of these animals permitted more satisfactory studies of metabolism than have been possible heretofore on adrenalectomized animals.

Fatty Degeneration of the Liver in Pancreatic Diabetes.—Long and Lukens [73] observed in cats that fatty infiltration and degeneration of the liver followed total pancreatomy, even though enough insulin was provided to control the diabetes. However, in cats that previously had been either hypophysectomized or adrenalectomized, this disturbance of the liver did not occur. Denervating the adrenal glands or removing only the medulla did not prevent it, and from this they presumed that the adrenal cortex was responsible for the fat in the liver and the degeneration of the liver that usually characterize pancreatic diabetes and that this action of the adrenal glands depended on the presence of the hypophysis.

The observation that animals (depancreatized dogs) adequately treated with insulin undergo fatty infiltration and degeneration of the liver and then die was made by the first investigators to use insulin experimentally.[83] The disturbance could be prevented by feeding raw pancreas to these diabetic animals, and later Best [84] showed that feeding lecithin, choline or betaine also would prevent the disturbance. An important observation was reported this year by Dragstedt, Van Prohaska and Harms.[85] These investigators confirmed the fact that the removal of the pancreas caused the fatty disease of the liver in question and that it was not due to the absence of pancreatic juice. It was not observed in normal dogs with a complete pancreatic fistula or in dogs after the pancreatic ducts had been ligated, and administration of active pancreatic juice was not of any avail. From 100 to 1,100 cc. of fresh pancreatic juice was administered daily without benefit, but it was found that 25 Gm. of fresh beef pancreas fed daily would both prevent or cure the abnormality and permit survival of the animal. Ten grams of fresh beef pancreas was not sufficient, and boiled pancreas was ineffective. An extract from fresh beef pancreas was made, and its admin-

83. Allan, F. N.; Bowie, D. J.; MacLeod, J. J. R., and Robinson, W. L.: Behavior of Depancreatized Dogs Kept Alive with Insulin, Brit. J. Exper. Path. **5**:75-83 (April) 1924.

84. Best, C. H.; Ferguson, G. C., and Hershey, J. M.: Choline and Liver Fat in Diabetic Dogs, J. Physiol. **79**:94-102 (July 28) 1933.

85. Dragstedt, L. R.; Van Prohaska, John, and Harms, H. P.: Observations on a Substance in Pancreas (a Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, Am. J. Physiol. **116**: 36-37 (June) 1936; The Relation of Pancreatic Juice to the Fatty Infiltration and Degeneration of the Livers of Depancreatized Dogs, ibid. **116**:122-123 (June) 1936.

istration prevented fatty infiltration and degeneration of the liver and cured the disturbance after it had developed. The extract was fat free, and thus its action could not be attributed to lecithin. Nor was it due to choline, because doses of choline that were several times as large were ineffective. The active derivative of the pancreas was prepared by extracting the pancreas with 95 per cent alcohol, afterward evaporating the alcohol filtrates at room temperature, drying the residue and washing it several times with several volumes of ether. The product was effective when administered orally in amounts corresponding to 100 Gm. of beef pancreas.

The clinical bearing of fatty degeneration of the liver in pancreatic diabetes and its prevention by the various means suggested are not immediately apparent. Diabetes in man seldom depends either on complete destruction of the pancreas or on suppression of its external secretion, and, so far as I know in the few cases in which this may be true, fatty degeneration of the liver has not been demonstrated. In 2 cases in which diabetes was associated with lesions of the pancreas resulting in steatorrhea recently studied at the Mayo Clinic by Bargen, Bollman and Kepler,[86] no clinical evidence could be obtained of disturbed function or other abnormality of the liver. On the other hand, a large (fatty?) liver is seen occasionally in cases of diabetes mellitus in which the external function of the pancreas apparently is intact. Hansen,[38] as has been mentioned, reported a number of instances of this abnormality in young diabetic patients but found in every case that the liver diminished in size after a period of treatment with protamine insulin. This suggests that the discontinuous action of insulin, when readily soluble (regular) insulin is given by infrequent injection, may be responsible for the hepatic degeneration of depancreatized animals and that pancreas and derivatives of pancreas given by mouth could owe their curative and preventive properties to some action whereby a more continuous insulin effect is maintained.

Fatty degeneration of the liver grossly similar to that obtained in diabetic animals has been reported by Judd, Kepler and Rynearson [87] in cases of severe chronic hypoglycemia. Two patients were subjected to exploratory operations, and specimens of the liver were removed for histologic examination. No tumor (insular adenoma) could be found. These patients were not benefited by treatment with choline or betaine.

86. Bargen, J. A.; Bollman, J. L., and Kepler, E. J.: The "Diarrhea of Diabetes" and Steatorrhea of Pancreatic Insufficiency, Proc. Staff Meet., Mayo Clin. **11**:737-742 (Nov. 18) 1936.

87. Judd, E. S.; Kepler, E. J., and Rynearson, E. H.: Spontaneous Hypoglycemia: Report of Two Cases Associated with Fatty Metamorphosis of the Liver, Am. J. Surg. **24**:345-363 (May) 1934.

Glyconeogenesis.—Among the evidence frequently quoted as supporting the theory of glyconeogenesis from fatty acids is that presented by Chaikoff and Weber.[88] They injected epinephrine into depancreatized dogs during fasting and recovered from the urine a larger amount of dextrose than they could account for on the assumption that the only endogenous source of dextrose is from protein, the glycerol of fat and the glycogen present in liver and muscle. Bollman, Mann and Wilhelmj,[89] repeating this work, determined the glycogen content before and after injecting epinephrine and reported that the "extra glucose obtained was equal to the amount of glycogen removed from the muscle." Bachrach, Bradley and Ivy [90] again have repeated the experiment, conducting it exactly as originally described by Chaikoff and Weber and using Chaikoff and Weber's values for the maximal amount of glycogen to be found in the liver and muscle of depancreatized dogs

Tabulation of Results, Adapted from Bachrach, Bradley and Ivy

Observers	Number of Dogs	Pre-Epinephrine Dextrose-Nitrogen Ratio	Nitrogen Excreted During Epinephrine Period, Gm. per Kg.	Dextrose Excreted During Epinephrine Period, Gm. per Kg.	Extra Dextrose in Epinephrine Period, Gm. per Kg.
Chaikoff and Weber	7	6.5	0.41	4.9	3.1
Bollman, Mann and Wilhelmj	4	3.2	0.39	2.2	1.2
Bachrach, Bradley and Ivy	14	2.4	0.41	2.4	1.8

after three days of fasting. All the dextrose excreted under the influence of epinephrine could be accounted for without postulating the formation of any dextrose from fat.

The accompanying table shows that the discrepancy between the results of Chaikoff and Weber and those of the later investigators is largely contributed to by the dextrose-nitrogen ratio for the period immediately preceding the administration of epinephrine. The average dextrose-nitrogen ratio for this period obtained by Chaikoff and Weber was extraordinarily high (6.5). The amounts of nitrogen found by all the observers were similar, and the differences all lie in the amount of dextrose excreted. This indicates that the animals of Chaikoff and

88. Chaikoff, I. L., and Weber, J. J.: The Formation of Sugar from Fatty Acids in the Depancreatized Dog Injected with Epinephrine, J. Biol. Chem. **76**: 813-832 (March) 1928.

89. Bollman, J. L.; Mann, F. C., and Wilhelmj, C. M.: The Origin of Glucose Liberated by Epinephrine in Depancreatized Animals, J. Biol. Chem. **93**: 83-91 (Sept.) 1931.

90. Bachrach, W. H.; Bradley, W. B., and Ivy, A. C.: Effect of Epinephrine on Glucose Excretion in Fasted Depancreatized Dogs, Am. J. Physiol. **117**: 203-205 (Oct.) 1936.

Weber had not reached a fasting level and that stored glycogen was contributing a larger share of the extra dextrose than they estimated. Thus honors still rest with Minkowski in this never ending controversy as to whether diabetes depends on the deficient utilization or the excessive formation of sugar.

Exercise and Carbohydrate Tolerance.—Courtice and Douglas [91] studied the effects of long walks on the metabolism of 2 subjects (themselves), the standard exercise being 10 miles (16 kilometers) at a rate of 4½ miles (7 kilometers) per hour. They observed that the respiratory quotient showed a rise in the early stages of the walk, enough to account for a consumption of 100 Gm. of carbohydrate. During the rest that followed the walk it fell to average figures, between 0.76 and 0.73; it remained low for three hours and in one experiment for nine and a half hours. This was accompanied with moderate ketosis, which had not appeared during the walk. A diet high in carbohydrate when given the day before the experiment prevented such ketosis, but giving more carbohydrate the morning of the exercise and a normal diet the day before did not. The respiratory quotient never fell so low as to afford indubitable evidence of the formation of sugar from fat.

In the rest period after exercise in these studies the sugar content of the blood never fell below normal limits, but the injection of sucrose, dextrose or fructose gave evidence of a reduced tolerance for sugar. It was therefore concluded that the function of the endocrine organs associated with carbohydrate metabolism may be correlated with the varying activity of the muscles and so afford a partial explanation of the changes in carbohydrate metabolism which result from severe exercise.

Dehydration in Diabetes.—Formerly it was assumed that the dehydration of diabetes could be attributed exclusively to glycosuria. When the concentration of dextrose in the blood exceeded a given threshold value, sugar was excreted by the kidneys and carried water with it. Certainly this was shown to occur; indeed, extreme dehydration could be produced when solution of dextrose was injected by vein into normal dogs at a rate exceeding the rate of utilization. This information was obtained from an elaborate series of experiments performed years ago by Woodyatt and his associates. More recently, as more came to be known about the rôle of ions of sodium in the metabolism of water, the loss of water in diabetic acidosis came to be explained on the basis of ketonuria. The ketones, being acids, are eliminated as salts of sodium, and loss of water follows the loss of base. Now, Himwich and Faze-

91. Courtice, F. C., and Douglas, C. G.: The Effects of Prolonged Muscular Exercise on the Metabolism, Proc. Roy. Soc., London, s.B **119**:381-439 (March 2) 1936.

kas [92] have reported experiments showing that the dehydration in diabetes may occur without ketonuria. Partly depancreatized dogs were given carbohydrate, fat and protein in amounts sufficient to maintain caloric equilibrium and insulin in doses adequate to prevent glycosuria. The protein content and the total base of the serum and the oxygen capacity of the blood, as well as the nitrogen, dextrose, total base and ketone content of the urine, were determined. Then the amount of dextrose in the diet was increased enough to produce glycosuria uncomplicated by ketonuria. The animals sustained a loss of weight associated with an increase in the volume of urine and a loss of base in the urine. That the loss of weight was due to dehydration could be told by the increased protein content of the serum and the raised capacity for oxygen of the blood. Subsequently, after an increase in the amount of sodium chloride in the diet the body was rehydrated as the deficit of sodium was corrected. Thus, although the mechanism of dehydration in diabetes may depend primarily on glycosuria, the importance of the part played by sodium is again emphasized.

HEMOCHROMATOSIS

The literature contains only a few scattered references to estimations of the iron content of the blood in cases of hemochromatosis, none being more recent than 1921. The technics employed have been improved. Therefore, the determinations made by Sachs, Levine and Griffith [93] are important. Their studies of the blood of 200 normal men and women, using the method of Wong, indicated for the men an average content of 50 mg. of iron per hundred cubic centimeters, with a range of from 40.05 to 58.6 mg. and a probable error of 2.56 mg. The figures for women were lower, showing a range from 33.45 to 49.25 mg., with an average of 42.67 mg. and a probable error of 2.13 mg. per hundred cubic centimeters. In 3 cases of hemochromatosis in men (1 doubtful as to diagnosis) the values for iron ranged from 88.9 to 74.4 per cent of these average figures. The copper content of the blood exceeded the normal average by from 9.8 to 18.2 per cent. This increase for copper was within the normal range and in view of the small number of cases was not thought to be significant.

92. Himwich, H. E., and Fazekas, J. F.: A Mechanism of Dehydration in Diabetes, Am. J. Physiol. **116**:75-76 (June) 1936.

93. Sachs, Adolph; Levine, V. E., and Griffith, W. O.: Blood Iron and Copper in Hemochromatosis, Proc. Soc. Exper. Biol. & Med. **35**:332-335, 1936.

Book Reviews

Exploration radiologique des colons et de l'appendice au moyen des solutions floculantes: Images de muqueuses. By George Maingot, Raymond Sarsin and Henri Dulcos. Price, 200 francs. Pp. 229, with 203 illustrations. Paris: Masson & Cie, 1935.

From a roentgenologic study of the colon and appendix much valuable information can be obtained regarding these organs which could not be obtained in any other manner. In order to enhance the value of such a study, it is necessary to employ the correct technic in examining these organs and to have a clear understanding of the normal roentgenologic appearance of these organs and the variations within the normal.

This monograph, prefaced by an excellent dissertation by Dr. Antoine Bécleré, eminent French roentgenologist, clearly explains the modern methods employed in examining the colon and appendix by means of the roentgen rays. The authors explain the roentgen aspects of the anatomy and physiology of the colon and appendix. Their study of the intestinal mucosa by means of colloidal thorium dioxide injected into the bowel is most interesting. After the injection of this opaque medium the colon is examined (1) under pressure, (2) after the elimination of most of the medium and (3) after the injection of air. They believe that there is a precipitation of the thorium dioxide on the mucosa of the intestine and that in this manner certain features of the mucosa are brought out in relief which could not be obtained in any other manner. Thorium, a radio-active element, owing to its high atomic number and specific density has a high absorbability rate for the roentgen ray. In the form of the dioxide it has been used in visualizing the hemoptic and lymphatic systems, and it has been used also in ventriculography and urography.

The authors have divided their book into four parts: the first part deals with technic, the second with symptomology, the third with syndromes and the fourth with the appendix. The chapter on the appendix is especially interesting and instructive. Those who still believe that the roentgen rays can offer little in the diagnosis of a chronic disorder of the appendix will profit greatly by reading this chapter, and only the most skeptical will fail to become convinced of its usefulness in this regard.

There is an extensive bibliography appended which represents the work of the best known roentgenologists of Europe and America. Singularly, however, the master of them all has been left out, namely, the late Russell Carmen, of the Mayo Clinic. The authors could have profited much by consulting the numerous works which Carmen published on the gastro-intestinal tract.

The book, which is easy to read and contains numerous beautiful illustrations, represents much labor and skill in its construction.

Experimental Studies on a Transmissible Myelomatosis (Reticulosis) in Mice. By Otto Kaalund-Jørgensen. Translated into English by Robert Fraser. Price, 12 kroner. Pp. 142, with 25 illustrations. Copenhagen: Levin & Munksgaard, 1936.

This monograph combines an excellent review of the literature concerning leukotic conditions in mice and guinea-pigs and the results of extensive and thorough experiments by the author. It has been fairly well established in the literature that leukosis in fowls can be transmitted by cell-free filtrable agents and that transmissible leukosis and filtrable sarcoma of fowls have many properties in common. Mammalian leukosis has, however, been transmitted only by means of living cells. The overwhelming majority of the transmissible mammalian leukoses hitherto described either have been or have been conceived as being lymphatic. Only in the last year or so (Furth and others) have reports appeared showing the existence of transmissible myeloid leukosis in mammals. The author's experi-

ments are concerned with the transmissibility of myeloid leukosis (myelomatosis). The use of mice of genetically pure strains is important for successful transmission. However, insusceptibility to implantation of leukotic cells can in many cases be overcome by general exposure of the animal to roentgen rays previous to inoculation. This makes it possible to use mice of unrelated strains. The author has succeeded in transmitting myelomatosis from mice to irradiated rats. His proof of the impossibility of transmitting myeloid leukemia by cell-free agents is convincing. It is shown that myelomatosis can be transmitted by an extremely small number of cells (about eight) and that the disease becomes systemic a short time after inoculation. The determination of the lethal roentgen dose for myelomatosis (3,100 to 3,700 roentgens) and the description of the technic and roentgen dose used for increasing the susceptibility of mice to transmissible leukosis are valuable. The neoplastic nature of mammalian leukosis is well supported, and the author believes that all human leukosis may well be due to neoplastic processes in the hematopoietic system.

There are twenty-four excellent photomicrographs in this book; the one colored plate might have been omitted. Robert Fraser, the English translator of this work, is to be congratulated, as are also the publishers. This monograph is indispensable to any one interested in experimental leukosis.

An Index of Treatment. By various writers, edited by Robert Hutchinson, M.D. Eleventh edition. Price, $12. Pp. 1035, with 147 illustrations. Baltimore: William Wood & Company, 1936.

The first edition of this index appeared in 1907, and evidently the work has since had a successful life of twenty-nine years, for new editions have been forthcoming at appropriate intervals in an effort to keep it up to date. American medical men, on the whole, have not been too enthusiastic over it. In the book's early days, for example, *The Journal of the American Medical Association* (**50**:2148 [June 27] 1908) greeted it coldly: "The work is intended to provide the practitioner with a complete guide to treatment, and the services of a large number of eminent authors whose names carry weight with English-speaking physicians have been made use of. The result is as satisfactory as a book constructed on this plan can well be." The reviews of subsequent editions have been equally lukewarm.

On the other hand, in England the "Index" appears to be more generally liked. The *British Medical Journal* has recently said of the latest edition: "During nearly three decades this well known source of reference has gained an established hold in confidence on the profession. Once again Dr. Robert Hutchinson must be warmly congratulated on his critical acumen as editor and on his success in literature and medicine. The Index is assured of continuing popularity."

One gathers, therefore, that there is a difference of opinion on the two sides of the Atlantic regarding the value of a compendium of this kind. Admittedly, it is well put together, with articles written by distinguished clinicians, and well edited. As a textbook of treatment, however, most American teachers will continue to look askance at it and to describe it, a little superciliously, as being "as satisfactory as a book constructed on this plan can well be."

The Specificity of Serological Reactions. By Karl Landsteiner, M.D. Price, $4. Pp. 178. Springfield, Ill.: Charles C. Thomas, Publisher, 1936.

This modest book is a most commendable and systematic presentation and discussion of the basic factors of immunity and resistance. The author has kept consistently to fundamentals and has analyzed them in clear terms. This is the first concise analysis of the work that has been done on the basis of the present knowledge of the chemical specificity of the fundamental factors of the immunologic Trinity—the antigen, the binding substance and the substrate. The evidence is reviewed that proves "that serologic properties are intimately connected with chemical constitution." The bibliography of the basic research and the index make this small book a necessary and useful reference tool for workers in the field of immunology.